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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors. This online publication has been corrected. The corrected version first appeared at thelancet.com on July 3, 2015.

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SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to provide readers with additional information.

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1. Authors and affiliations

The paper was submitted by the RTS,S Clinical Trials Partnership.

2. Supplementary methods

2.1. Ethical considerations

This phase III, double-blind (observer-blind), individually randomized, controlled multicentre trial was performed in 11 sites across sub-Saharan Africa. The study design and rationale for selection of endpoints have been described previously.[1] Overall this study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, the principles of Good Clinical Practice[2] and with the local rules and regulations of each country. The study was monitored by the sponsor, GlaxoSmithKline (GSK) Biologicals SA (GSK monitors or outsourced monitors from Quintiles [Quintiles, Centurion, South Africa] contracted by GSK Biologicals SA), and overseen by a formally constituted Independent Data Monitoring Committee (IDMC), that reviewed, among other information, unblinded comprehensive safety data every three months to authorize study continuation. The IDMC conferred before the initiation of the study and had three-monthly teleconferences and one annual meeting thereafter. A Local Safety Monitor, who was an experienced clinician not taking part in the study, was available at each study site to support the clinical investigators and to act as a link between the investigators and the IDMC. The study protocol and amendments, consent forms, and other information that required pre-approval were reviewed and approved by a national, regional, or research centre ethics committee (EC) or institutional review board (IRB) in accord with local requirements. A list of all EC/IRBs is provided in Table S1a.

2.2. Roles of investigators and sponsor

The study was sponsored by GSK Biologicals SA, the vaccine developer and manufacturer, and funded by both GSK Biologicals SA and the PATH Malaria Vaccine Initiative (MVI).The study was designed by the Clinical Trials Partnership Committee (CTPC), consisting of representatives of all contributing research centres, study sponsor and study funders (as detailed in Leach et al.[1]). All authors were involved in data collection. All data were analysed following a pre-defined analysis plan. The CTPC had full access to the study data, made the decision to publish the manuscript in its current form, and supervised the writing of the manuscript.

2.3. Study sites and affiliated partners

The study was conducted in 11 study sites located in seven countries in sub-Saharan Africa together with their partner institutions. The study sites represent the range of malaria transmission seen across sub-Saharan Africa (Figure 1 in the paper). The list of study sites and their partners is provided in Table S1b.

2.4. Screening and informed consent

Two age categories of children were eligible for inclusion in the trial. One age category comprised infants who were 6-12 weeks of age (inclusive) at the time of first vaccination and who had not previously received a dose of vaccine against diphtheria, tetanus, pertussis or *Haemophilus influenzae* type b. The other age category comprised children 5-17 months of age (inclusive) at the time of first vaccination. Screening procedures included a review of a child's medical history, a physical examination and a blood test for assessment of haemoglobin concentration. The main exclusion criteria were: moderate or severe illness at the time of enrolment, a major congenital defect, malnutrition requiring hospitalization, severe anaemia - defined as a haemoglobin concentration < 50 g/L or a haemoglobin concentration < 80 g/L associated with clinical signs of heart failure or severe respiratory distress, or a past history of a neurological disorder or of an atypical febrile seizure. A past history of a simple febrile seizure was not an exclusion criterion. Children with active HIV disease of Stage III or Stage IV severity, as defined by the World Health Organization, at the time of screening were excluded.[3] A previous history of active Stage III or Stage IV HIV disease was not an exclusion criterion. Routine testing for HIV was not done in this study. HIV positivity was reported on the general medical history taken at screening or identified by morbidity surveillance during the study. The decision to report a new HIV infection depended on the investigators

judgment as to whether it met the criteria for a serious adverse event. Likewise, it was at the investigators discretion whether to perform antibody or PCR confirmatory testing. Voluntary counselling and testing, highly active anti-retroviral therapy (HAART) and prevention of mother to child transmission (PMCT) were available at all study sites according to national policies.

Prior to enrolment, study teams conducted a series of information activities. Study teams held discussion meetings with the administrative leaders and/or community leaders. They described the outline of the proposed study, paying particular attention to study procedures, including screening of children, immunization, blood collection, follow-up and their associated risks. Following community meetings, and a positive recommendation from community leaders, the parent(s)/guardian(s) of children in the eligible age categories were approached. The need for a vaccine against malaria was discussed and the objectives of the study were explained. The study procedures were described carefully, including the blinding of study treatment, the immunization and blood collection. Parent(s)/guardian(s) interested in enrolling their child into the study were invited to the screening visit. At the screening visit, the site investigator or his/her designate described the protocol to the parent(s)/guardian(s) face to face or the informed consent information was presented to groups at an initial information session. Information was provided in both an oral and a written form in a language fully comprehensible to the child's family. Each child's family had the opportunity to inquire about details of the study and ask any questions individually in a private place. Formal informed consent was obtained from each child's parent(s) or guardian(s) prior to the performance of any study-specific procedures. Literate parent(s)/guardians willing to let their child enter into the study were asked to sign and date the informed consent form (ICF). If the parents or guardians were illiterate, the study and the ICF were explained point by point in the presence of an impartial witness. The impartial witness could be a friend or family member accompanying the parents or any other literate person independent from the study team. Parent(s)/guardian(s) confirmed their consent for their child to take part in the study by marking the ICF with their thumbprint and the impartial witness personally signed and dated the ICF.

During the course of the study, the protocol was amended to extend the follow-up of study participants. The study includes a primary phase of approximately 32 months for each subject (+ one month of screening) and an extension phase that continued the follow-up until end December 2013. Parents/guardians of subjects who had received at least one dose of study vaccine or comparator vaccine in the primary study phase and whose first extension visit took place before (and including) 30 September 2013 were invited to enrol their child into the extension phase. Freely given informed consent was obtained from subjects' parent(s)/guardian(s) prior to participation in the extension.

2.5. Randomization and blinding

After verification of eligibility criteria, and prior to first vaccination, a unique treatment number was assigned to each participating child. Participating children from each age category were randomized into one of three study groups according to a 1:1:1 ratio (R3R, R3C or C3C) using a randomization algorithm with SAS version 9.1. Randomization was stratified for age category using study site as a minimization factor, ensuring balanced treatment allocation within each study site. All children's parent(s)/guardian(s) were provided with a study identification card with a photo of their child, the child's name and a unique subject number. All data were collected using remote data entry and electronic case report forms.

Data were collected in a double-blinded (observer-blind) manner; the vaccinated children and their parent(s)/guardian(s) as well as those responsible for the evaluation of study endpoints were unaware of whether RTS,S/AS01 or a comparator vaccine had been administered to a particular child. The vaccines used in this study were of different appearance. The content of the syringe was, therefore, masked with an opaque tape to ensure that parent(s)/guardian(s) were blinded. The only members of study staff who knew of the vaccine assignment were those responsible for preparation and administration of vaccines; these staff played no other role in the study except screening or collection of biologic specimens.

2.6. Study vaccines

Each child received a primary schedule of three doses of either the candidate malaria vaccine RTS,S/AS01 or a comparator vaccine. In the 5-17 months age category, the comparator vaccine for the primary series was a rabies vaccine VeroRab™ (Sanofi-Pasteur) and in the 6-12 weeks age category the comparator

vaccine was a meningococcal C conjugate vaccine Menjugate™ (Novartis). Participants in both age categories received a booster dose of either RTS,S/AS01 (in the R3R group) or Menjugate™ (R3C and C3C groups) 18 months after the third dose of the primary schedule. Vaccines for the primary series were administered intramuscularly into the left deltoid of children in the 5-17 months age category and into the left anterolateral thigh of infants in the 6-12 weeks age category. Booster doses were administered into the left deltoid for all participants. The choice of comparator vaccines was guided by the principles of benefit to the control group without compromising the evaluation of clinical study endpoints. Infants enrolled in the 6-12 weeks age category received the RTS,S/AS01 or comparator vaccine at the same time as DTPwHepB/Hib pentavalent vaccine (Tritanrix™ HepB/Hib, GSK group of companies), which was administered into the right anterolateral thigh, and an oral polio vaccine containing serotypes 1, 2 and 3 (Polio Sabin™, GSK group of companies).

The RTS,S/AS01 candidate vaccine has been developed and manufactured by GSK Vaccines and is designed to protect against *Plasmodium falciparum* malaria. Manufacturing and quality control are performed in line with current Good Manufacturing Practices. No quality issues in the vaccines used in this study were recorded. “RTS,S” comprises the carboxyl terminal portion (amino acids 207 to 395) of the circumsporozoite protein from the NF54 strain of *P. falciparum* fused to the hepatitis B surface antigen, co-expressed in yeast with non-fused hepatitis B surface antigen."AS01" describes the Adjuvant System comprising liposomes, MPL (3-O-desacyl-4’-monophosphoryl lipid A) and QS-21[1] (a triterpene glycoside purified from the bark of *Quillaja saponaria*). Each dose of reconstituted RTS,S/AS01 (0.5 mL) contains approximately 25 µg of antigen, 25 µg of MPL and 25 µg of QS-21 with liposomes.[4]

Sanofi-Pasteur’s chromatographically purified Vero cell culture rabies vaccine VeroRab™ is based on the inactivated Wistar Rabies PM/W138 1503-3M strain and it is given in a ≥2.5 IU/0.5 mL dose.

One dose (0.5 mL) of Novartis’s meningococcal C conjugate vaccine contains 10 µg *Neisseria meningitidis* (strain C11) group C oligosaccharide conjugated to 12.5-25 µg *Corynebacterium diptheriae* CRM_{197} protein adsorbed on aluminum hydroxide (1.0 mg). The excipients of the reconstituted vaccine include mannitol, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride and water for injections.

GSK Vaccines’ DTPwHepB/Hib vaccine is prepared by reconstitution of the Hiberix™ pellet with the Tritanrix™ HepB suspension. Each 0.5 mL dose contains not less than 30 IU of adsorbed diphtheria toxoid, not less than 60 IU of adsorbed tetanus toxoid, not less than 4 IU of whole cell pertussis, 10 µg of recombinant hepatitis B antigen (HBsAg) protein and 10 µg of purified capsular polyribosyl ribitol phosphate covalently bound to approximately 30 µg tetanus toxoid. Tritanrix™ HepB also contains 2-phenoxyethanol, polysorbate 20, sodium chloride, thiomersal and water for injection. Hiberix™ also contains lactose.
The oral polio vaccine obtained from GSK Vaccines is a stabilized suspension of types 1, 2 and 3 live attenuated polioviruses (Sabin strains): Type 1 (strain LSc, 2ab), Type 2 (strain P 712 ch, 2ab), Type 3 (strain Leon 12a, 1b). The excipients comprise magnesium chloride, L-arginine, polysorbate 80, neomycin sulphate (residual), polymyxin B sulphate (residual) and purified water.

Children were observed closely for at least 30 minutes after vaccination, with appropriate medical treatment and equipment readily available in case of an anaphylactic reaction. A study clinician accredited in paediatric resuscitation was available at all vaccination sessions.

2.7. Bednets and indoor residual spraying

The research team ensured that insecticide treated bednet use was optimized in each study population. At study start in two study sites (Kilifi, Kenya and Bagamoyo, Tanzania) this was achieved through close collaboration with the respective National Malaria Control Programmes. In the other sites, impregnated bednets were distributed by the study teams to all children who underwent screening, regardless of whether

[1] QS-21 is licensed from Antigenics Inc, a wholly owned subsidiary of Agenus Inc.

they were eligible for the study. During the course of the study three sites (Agogo, Siaya and Lilongwe) replaced any damaged nets upon the parents' request. Other centres relied upon the National Malaria Control Programme for the ongoing replacement of bednets.

Data were collected on malaria control measures used by the participants' families during the period of surveillance. Bednet usage and indoor residual spraying were documented 12 months and 29 months after the third vaccine dose had been given and also one month before the end of the extension phase. Study children's parents were asked if their house had been sprayed with a residual insecticide and, if so, when this was done. Then they were asked if their child sleeps under a bednet. During a home visit, a field worker inspected the child's bednet and the integrity of the net was recorded as follows: 1- no bednet; 2- impregnated bednet with no hole large enough to admit three fingers; 3- impregnated bednet with at least one hole large enough to admit three fingers; 4- untreated bednet with no hole large enough to admit three fingers; 5- untreated bednet with at least one hole large enough to admit three fingers.

2.8. Safety assessment

During the study, investigators or their designates were responsible for documenting and reporting events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE). Parents/guardians of children participating in the study were requested to contact study personnel immediately if their child showed any signs or symptoms they perceived as serious.

An adverse event was defined as any untoward medical occurrence in a child participating in the study temporally associated with vaccination whether or not it was considered to be related to the vaccine. An AE could, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with vaccination.

For the purpose of this study, a SAE was defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, or a seizure that occurred within 30 days of vaccination. Abnormal laboratory findings that were judged by the assessing clinician to be clinically significant were recorded as an SAE if they met the criteria for an SAE as defined above.

Seizures occurring within 30 days of vaccination and immune-mediated disorders occurring at any time during the study were reported as SAEs in order to ensure availability of full case narrative descriptions.[1] Data on seizures occurring within seven days following a dose of the primary vaccination series were collected and analysed according to the Brighton Collaboration guidelines[5] and have been published previously.[6,7]

Because paediatric auto-immune diseases are rare and may be underestimated in sub-Saharan Africa, training material on paediatric auto-immune disease presentation and diagnosis was provided by the study sponsor. A specific, standardized clinical data collection questionnaire was generated. Collaborations with reference laboratories in South Africa were initiated so that serum samples or histopathologic specimens could be sent to South Africa for analyses not available locally.

Diagnosis of all adverse events, including the diagnosis of meningitis, was based on all available clinical evidence and was not bound by stringent laboratory or diagnostic criteria. Efforts have been made both prospectively and retrospectively to confirm a diagnosis of meningitis on cerebrospinal fluid (CSF) samples whenever available, using biochemical, microbiologic and molecular testing as described in section 2.12 below. The IDMC also reviewed unblinded safety reports containing specific sections on seizures and meningitis.

In addition, the case histories of all participants with reported meningitis or other central nervous system (CNS) infections or inflammation were reviewed by two independent experts. Based on their judgement the experts classified the cases as definite meningitis or not meningitis; in case of no clear clinical picture and/or laboratory results interpretation the case was labelled undetermined.

Solicited AEs were reported for the period up to seven days after vaccination (day of vaccination and six subsequent days) following each vaccine dose for the first 200 infants enrolled at each study site. Local AEs solicited were: pain at the injection site; swelling at the injection site and redness at the injection site. Solicited general AEs were: drowsiness, fever; irritability/fussiness and loss of appetite. Grading for solicited AEs are presenting in Table S33. All unsolicited AEs were reported for 30 days following each vaccine dose for the first 200 infants enrolled at each study site.

SAEs were collected for all participating children throughout the study period, from the time of parental consent. At every visit/contact, information was sought on the occurrence of AEs/SAEs. SAEs were identified by surveillance at health facilities in the study area and through monthly home visits. All AEs that were observed directly or that were observed by a clinical collaborator, those that were identified through surveillance at health facilities in the study area or those reported by the child's parent/guardian spontaneously or in response to a direct question were evaluated. Assessments were made of the maximum intensity of all unsolicited AEs and SAEs during the period of the event. This assessment was based on the attending clinician's medical judgment. A grade was assigned to all adverse events as follows; grade 1 (mild) - an AE which was easily tolerated by the child, causing minimal discomfort and not interfering with everyday activities; grade 2 (moderate) - an AE which was sufficiently discomforting to interfere with normal everyday activities and grade 3 (severe) - an AE which prevented normal, everyday activities. SAEs were coded according to the MedDRA (Medical Dictionary for Drug Regulatory Activities). Non-malaria SAEs were defined as those which excluded the MedDRA terms "*Plasmodium falciparum* infection", "Malaria" and "Cerebral malaria".

Verbal autopsies were carried out on all children who died outside a health facility using a questionnaire based on the *International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (*INDEPTH) standard questionnaire, adapted to be locally appropriate.[8] To support the timely reporting of SAEs, diagnoses were made according to the usual processes of each study site.

At the end of the extension phase, all deaths were reviewed using all available information including SAE forms, verbal autopsy forms and information on meningitis cases provided by a panel composed of three investigators who are experienced verbal autopsy reviewers. Each death was reviewed by each of the three reviewers independently. They recorded 1) the disease or condition directly leading to death, 2) any morbid conditions leading to the condition that directly caused death and 3) any other significant conditions contributing to the death, but not related to the disease or condition causing it. Final diagnoses were based on the reviewer's medical/clinical judgment and were coded according to the ICD10 code at the three digit level. At the end of the independent review by the three panel reviewers, all records of individual reviewers were examined centrally by the Clinical Research and Development Lead (CRDL) and the Lead CRDL at GSK Vaccines. If a minimum of two reviewers were in agreement, a cause of death was ascribed. If there was no agreement between the three reviewers, a consensus meeting was held where an agreement was reached wherever possible. If the joint panel was unable to reach a consensus the cause of death was recorded as unknown (coded R99).

2.9. Surveillance for clinical and severe malaria episodes

During the informed consent process, parents were asked to bring their child to a study health facility as soon as possible if their child fell sick during the study. Malaria was captured by passive case detection. Passive case detection (PCD) is the detection of malaria disease by self-presentation to health facility in the study area. All participating children who presented to a health facility in the study area were evaluated as potential cases of malaria using a standardised algorithm. All parents were asked whether the child had had a fever within the previous 24 hours and all children had their temperature measured. A blood sample was taken for testing for malaria parasites in all children who had had a history of fever during the previous 24 hours or who had a measured axillary temperature $\geq 37.5°C$ at the time of presentation.

Children who needed inpatient treatment were provided transport to a hospital participating in the study. All participating children who presented for admission were evaluated as a potential case of severe malaria following a predefined algorithm (Table S2). Methods for detection and management of severe malaria in children enrolled in the trial have been described in detail by Vekemans et al.[9] During any hospitalization, the child's course was monitored to capture the clinical signs and blood parameters indicative of

progression to severe malaria. If a child's condition deteriorated following admission, additional investigations were performed.

Treatment of malaria was conducted in accordance with national guidelines. Overall, 99% of children and young infants who presented with confirmed malaria to study clinics received treatment with artemisinin combination therapy (ACT) (Figure S3). In eight of the 11 study sites, the first line treatment for uncomplicated malaria was artemether-lumefantrine whilst in the three other sites (Agogo and Kintampo, Ghana; Nanoro, Burkina Faso), it was artesunate-amodiaquine. The study protocol specified that children admitted to hospital with severe malaria would receive intravenous quinine. During the course of the study, information on the superiority of artesunate over quinine for the treatment of severe malaria became available and as this change in treatment was introduced at country level, artemisinin preparations were used in preference to quinine.[10]

2.10. Chest radiographs

Chest radiographs were obtained as part of the standardized evaluation of study participants brought to a healthcare facility with tachypnea, lower chest wall indrawing, abnormally deep breathing, or if a study clinician considered this to be an appropriate investigation.[9] A digital radiography system was provided to each study site to facilitate radiological assessment of study participants. The radiographers and the physicians who read the images for the study endpoints received standardized technical training by the manufacturer of the radiography equipment and training on interpretation of chest radiograph images was provided by expert radiologists and physicists. To ensure a robust and verifiable data base of radiographs, quality control systems that included local on-site training, development of quality manuals, quality control checks, on-site radiology committees and external audits were implemented. Digital images were anonymized and sent to a central repository at GSK Vaccines via a satellite internet connection.

For the purpose of endpoints assessment, and to ensure accurate diagnosis of pneumonia, a process developed by WHO[11] was followed. Each radiograph was read independently by a clinician attached to the centre where the radiograph was taken, and by an external radiologist. GSK Vaccines reviewed all readings made by the centres and by the external radiologists and any images with discordant readings were sent to another panel of radiologists for a final reading. The reporting of pneumonia as a SAE was made based on clinicians' judgment and independent of this protocol-specific assessment. Clinicians and external radiologists were trained in chest radiograph interpretation according to WHO guidelines.[11] Physician /radiologist who read the x-ray image had to pass by 80% the WebAims test before reading images for endpoint assessment.

2.11. Anthropometry

Length/height, weight and mid-upper arm circumference were measured at screening, one month, 18 months and 30 months after the third dose of vaccine in the primary study phase, at 42 months post third dose and at the last visit of the extension phase. Anthropometry was also measured during inpatient admissions. The methodologies used for anthropometry were adapted from Cogill.[12]

2.12. Laboratory analyses

The development of standardized laboratory methods and quality control processes for this study have been described fully in a separate publication[13] and are only summarized briefly here.

- ***P. falciparum*** **counts by blood smear**

All slides were read independently by two trained microscopists. A third independent microscopist read the slide if any of the following discrepancies between the first two readings occurred: (1) a positive reading by one microscopist and a negative reading by the other; (2) both microscopists recorded a parasitemia >400 parasites/μL but the higher count divided by the lower count was >2; (3) at least one microscopist recorded a parasitemia ≤400 parasites/μL but the higher reading was more than 10 times the lower reading. If the initial two readings gave concordant results, the final parasite density was considered to be the geometric mean of these two readings. If the readings were discordant, then the following principles were applied: (1) where one reading was positive and the other negative, the majority decision obtained following the

reading by the third microscopist was adopted and, when the slide was considered positive, the parasite density was recorded as the geometric mean of the two positive results; (2) when all three readings were positive, the final result was the geometric mean of the two closest readings (on a log scale). As a quality measure, agreement between the two microscopists was calculated by means of the Kappa statistic. Internal QC was performed on one negative and one positive slide for each batch of stain. The External QA process for slide reading comprised species identification and parasite quantification. Three assessments per year were carried out, including 20 samples per microscopist. Microscopists who were below the level defined as competent were considered to be 'in training' and were not allowed to read study slides until they were retrained and re-assessed.

- ***Haematology and biochemistry***

Automated biochemical and haematological methods were used. All biochemistry automated analysers were enrolled initially with International External Quality Assessment (EQA) but later switched to the programme run by the Royal College of Pathologists of Australia, because the latter was more appropriate for the study requirements at the time. All haematology automated analysers were enrolled in EQA. Each laboratory had to demonstrate method qualification for biochemistry and haematology, including analysis of repeatability, reproducibility, linearity, QC stability and accuracy between main and back-up analysers. Data were sent to GSK Vaccines for analysis and feedback was provided to laboratories. Daily internal QC was performed at each laboratory, and external quality control was performed monthly for biochemistry and haematology samples.

- ***Microbiology***

Standard microbiology methods for blood and CSF culture were followed using automated Bactec™ incubators and paediatric bottles (Bactec BD Diagnostic Systems, USA). Positive cultures were sub-cultured using standard methods.[14, 15] For the purpose of study analysis, as opposed to clinical care, results were classified by standardised case definitions based on an established methodology.[16] A blood culture was considered positive if a definite pathogen was isolated (e.g. *Streptococcus pneumoniae*, *S. agalactiae*, *S. pyogenes*, *H. influenzae*, Salmonella species) or if a bacterium that could be either a pathogen or a contaminant was isolated within 48 hours of incubation (e.g. *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*). A blood culture was considered to be contaminated if a known contaminant was isolated or if a bacterium that could be either a pathogen or a contaminant was isolated after 48 hours of incubation.[16]

CSF was examined by Gram stain and a white cell count was performed using a haemocytometer. Direct agglutination methods using commercial kits (Remel Wellcogen Bacterial Meningitis Antigen Latex Kit or BIO-RAD Pastorex Meningitis Kit) were used for early detection in CSF of specific organisms like *S. pneumoniae*, group B streptococci, *H. influenzae* type b, *E. coli* and *Neisseria meningitidis* in CSF. In parallel, CSF was inoculated directly onto recommended culture media and into the same bottles used for blood culture in automated incubators to allow for bacterial growth, identification and antimicrobial sensitivity testing using the disk diffusion method.

For the assessment of protocol endpoints, bacterial meningitis was defined as the presence of a CSF white cell count of $\geq 50 \times 10^6$/L, a positive CSF culture of compatible organisms or a positive CSF latex agglutination test for either *H. influenzae* type b (Hib), *N. meningitidis* or *S. pneumoniae*.[9, 17] The reporting of a meningitis case as an SAE was independent of this definition. SAE diagnoses were made by the study clinicians using clinical judgment based on the clinical and laboratory evidence available. Microbiology quality assessment included evaluation of microscopy, culture, identification and antimicrobial susceptibility testing. Each laboratory received six samples (with at least two meningeal and two enteric organisms) three times per year, and the criteria of acceptability were defined by the National Institute of Communicable Disease (NICD, South Africa). Internal quality control was performed using American Type Culture Collection control strains for species identification every week, when a new batch of reagent was received or when discordant results were obtained. The contamination rate of the clinical specimens was evaluated monthly by internal assessment. Continuous assessment allowed re-training programmes for both clinical and laboratory staff and more intense quality evaluation when there was a high contamination rate.

2.13. Immunological assessment

During the primary study phase, anti-circumsporozoite (anti-CS) antibody titres were measured in the first 200 participants enrolled at each study site in each age category. During the extension phase, blood samples for the assessment of anti-CS response were collected in the first 200 participants in each age category in three study sites: Siaya, Agogo and Lilongwe.

Antibodies specific for the circumsporozoite protein tandem repeat epitope were assessed by a standard, validated ELISA with plates adsorbed with the recombinant antigen R32LR that contains the sequence [NVDP(NANP)15] 2LR as described previously.[18] Briefly, R32LR protein was coated onto a 96-well polystyrene plate. Serial dilutions of serum were added to the 96-well plate and, after incubation, the plates were washed and horseradish peroxidase conjugated polyclonal rabbit anti-human IgG was added. After a final washing step, a colour reaction was developed with 3, 3',5,5' tetramethylbenzidine and the plates were read in an ELISA reader. Antibody concentrations were calculated from a standard curve with the software SoftMax® Pro (using a four parameters equation) and expressed as EU/mL. Anti-CS antibodies were measured at the CEVAC Laboratory, University of Ghent, Belgium. The cut-off for the anti-CS ELISA was 0.5 EU/mL. Serum samples with a titre below the cut-off value were given a value of 0.25 EU/mL for the purpose of calculation of geometric mean titres.

2.14. Data collection and data management

At each study site, data were remotely entered on electronic case report forms and transferred to GSK Vaccines for data management. External monitors reviewed medical records, sample storage, and laboratory procedures to ensure data integrity.

2.15. Contribution to the per-protocol analyses

To be included in the per-protocol analysis of efficacy, participants enrolled in each age category must have received three doses of RTS,S/AS01 or comparator vaccine according to protocol procedures within specified intervals, and contributed to the time at risk in the follow-up period starting 14 days post dose 3. Participants unblinded by the safety department were also excluded from the per-protocol population for efficacy. In addition, participants in the 6-12 weeks age category must have received three doses of co-administered vaccine (DTPwHepB/Hib and OPV).

- Per-protocol population [M2.5-M32/SE]: N = number of subjects in the per-protocol population (as above) who received the primary schedule according to protocol.
- Per-protocol population [M21-M32/SE]: N = number of subjects in the per-protocol population [M2.5-M32/SE] who received the booster dose according to protocol.

To be included in the per-protocol analysis of immunogenicity, participants must have received all vaccinations according to protocol procedures. Subjects must also have followed protocol defined intervals for vaccinations and blood sampling schedules. Participants with protocol deviations in terms of administration of concomitant vaccinations (in the 6-12 weeks age category), screening procedures or participants unblinded by the safety department or investigators were excluded from the per-protocol analysis of immunogenicity.

2.16. Statistical methods for the analysis of efficacy at Month 32 and at the end of the extension

- ***Presentation of results by transmission intensity***

The incidence of clinical malaria meeting the secondary case definition (a measured or reported fever within the previous 24h and a parasite density >0 parasites per cubic millimetre) in infants in the control group measured over 12 months of follow-up was used to categorize malaria transmission across study sites. This measure was used because it most closely reflects force of infection and is less influenced by acquired immunity that might reduce the incidence of clinical malaria in older children. For all tables and figures, study sites are presented from the lowest to the highest incidence of clinical malaria.

- ***Vaccine efficacy against clinical malaria***

Vaccine efficacy against all episodes of clinical malaria was estimated as 1-IR where IR is the incidence ratio (total number of events/follow-up time in the RTS,S/AS01 group over the total number of events/follow-up time in the control group) calculated by negative binomial regression, allowing for interdependence between episodes within the same subject (mixed model with over-dispersion parameter estimated from the random effect) and presented together with 95% confidence interval (CI) and p-values calculated from this model. The data were structured so that each subject in the analysis has one record with follow-up time and the number of episodes observed. Then we fitted a negative binomial model by estimating the over-dispersion parameter as a random effect on the subject. As a result, we model between subject variation, and individual subjects are not forced to an overall over-dispersion parameter. VE estimates were unadjusted for covariates. Fourteen days following an episode which met the case definition under evaluation were subtracted from the follow-up time. Results are presented per site and overall. Overall estimates were adjusted for study site as a fixed effect, whereas site estimates were unadjusted for covariates. The p-value for the interaction term between site and group allocation was calculated.

- ***Vaccine efficacy against severe malaria, incident anaemia, malaria hospitalisation, fatal malaria and against other serious illnesses***

The incidence of severe malaria, malaria anaemia, malaria hospitalisation, fatal malaria, sepsis, hospitalised pneumonia, all-cause hospitalisation, all-cause mortality and blood transfusions in children in each study group was determined. VE was estimated as 1-RR where RR is the risk ratio (proportion of participants reporting the event in the RTS,S/AS01 group over the proportion in controls) over the entire follow-up period, and presented together with 95% CIs and p-values. Vaccine efficacy estimates were unadjusted for covariates.

- ***Vaccine efficacy against prevalent parasitaemia and prevalent anemia***

VE against prevalent endpoints (parasitemia, moderate and severe anaemia) was estimated as 1-RR where RR is the risk ratio (proportion of participants reporting events in the RTS,S/AS01 group over the proportion in controls) and presented together with 95% CIs and p-values. VE estimates were unadjusted for covariates.

- ***Vaccine impact***

The number of cases of clinical malaria, severe malaria, malaria hospitalisations, fatal malaria, all-cause hospitalisation, all-cause mortality, severe anaemia and blood transfusions averted overall was calculated. The number of cases of clinical and severe malaria averted was also calculated for each site. Cases averted were calculated in the ITT population. The number of cases averted was calculated as the difference in cases between the control group and the vaccine group (R3R+R3C up to the time of booster dose and R3R and R3C separately after the booster dose) with a 95% confidence interval. The number of cases averted over time were calculated as the difference of the estimated cases between the control group and the RTS,S/AS01 group. Estimated cases in each group were calculated as the area under the curve of the three-month incidence (all episodes) over time as:

$$\sum_{t=1}^{T}\left(\frac{all\ episodes_t}{person\ time\ at\ risk_t}\cdot \Delta time_t\right)$$

where T is the total follow-up time, t represents each one of the three-months periods, $all\ episodes_t$ is the total number of episodes in the period of time t, $person\ time\ at\ risk_t$ is the person follow-up time during the period t and $\Delta time_t$ is the duration of the period t (three months).

The number of cases averted was expressed as cases averted per 1000 subjects followed-up during the study period. Fourteen days following an episode were subtracted from the time at risk and no malaria events were counted during this period. The 95% confidence intervals of the difference in cases were estimated using bootstrap methodology using the 2.5 and 97.5 centiles of 1000 replicates.[19] Replicates were made sampling subjects stratified by category of the intensity of malaria transmission. To calculate the cases averted until Month 32, 11 periods of three months were used. To calculate the cases averted until the

end of the extension (SE), 16 periods of three months were used in the 5-17 months age category, and 13 periods of three months were used in the 6-12 weeks age category. These correspond to the median follow-up times until the end of the extension in these age categories. The more sensitive secondary case definitions of clinical malaria (a measured or reported fever within the previous 24 hours and a parasite density >0 parasites per cubic millimetre) was used for evaluation of the impact of RTS,S/AS01 on the burden of malaria because, in clinical practice, these children would receive treatment for malaria.

To evaluate the effect on growth, height for age, weight for age and mid arm circumference, z-scores for each age category as well as the absolute height at Month 32, Month 44 and at end of extension were tabulated and the mean values were compared between study groups using a t-test. For growth parameters, the evaluation at the end of extension was stratified between children who made their Month 32 visit on or before 30 June 2012 (SE [late]) and those whose Month 32 visit was after 30 June 2012 (SE [early]). Subjects in the SE early group did not undertake the Month 44 visit but progressed directly to end of extension scheduled around December 2013 for all subjects regardless time of enrolment.

2.17. Major protocol deviations

Deviations related to defaults in bednet distribution at screening and exposure of study vaccines to temperatures outside the recommended ranges were described in detail when the first results of this phase III study were reported.[6] These deviations did not pertain to participants enrolled in the 6-12 weeks age category. Also, during monitoring, it was found that one subject belonging to the 5-17 months age category was enrolled twice at two different clinics under two different subject numbers. This deviation was reported to the site EC/IRB. The subject was excluded from the per-protocol analyses. Due to the removal of one subject number from the database, the total number of subjects enrolled into the study changed from 15460 subjects (8923 in 5-17 months), as reported in previous analyses, to 15459 subjects (8922 in 5-17 months) in the final analyses reported here. Two field workers from Bagamoyo assigned to perform monthly home visits for the detection of unreported SAEs were suspected of not performing these visits and falsifying the visit reports. Probing the SAEs reporting rates in the potentially affected subjects and the non-affected subjects showed no evidence of under-reporting of SAEs. A sensitivity analysis (not shown here) excluding the potentially affected subjects has not resulted in any clinically meaningful difference and has, therefore, no impact on the overall interpretation of the relative incidence between RTS,S/AS01 recipients and controls in either age category or in the subgroups analyses affected (low weight for age, very low weight for age and pre-term infants) for any SAE MedDRA PT term.

2.18. Trademarks

3. Groups that have contributed to the delivery of this study

Writing group (September 2014): Salim Abdulla (Chair), John J Aponte, Brian Greenwood, Mary J Hamel, Dirk Heerwegh, Didier Leboulleux / David Kaslow, Amanda Leach, Marc Lievens, John Lusingu, Patricia Njuguna, Aurélie Olivier, Lucas Otieno, David Schellenberg, Marcel Tanner, Johan Vekemans.

Statistical working group: John J Aponte, Marc Lievens (Chair), Bruno Mmbando, Ali Mohamed Ali, John Williamson, Wasima Rida.

Clinical Trials Partnership Committee (September 2014): Salim Abdulla, Tsiri Agbenyega, Selidji Todagbe Agnandji, Pedro Aide, Pauline Akoo, Daniel Ansong, Kwaku Poku Asante (Co-Chair), Carla Botting, Umberto D'Alessandro, Samwel Gesase, Brian Greenwood, Yolanda Guerra, Mary J. Hamel, Tinto Halidou (Chair), Irving Hoffman, Portia Kamthunzi, Simon Kariuki, David Kaslow, Peter Gottfried Kremsner, Didier Lapierre, Amanda Leach, Didier Leboulleux, John Lusingu, Eusebio Macete, Kevin Marsh, Francis Martinson, Ali Mtoro, Patricia Njuguna, Bernhards Ogutu, Lucas Otieno, Walter Otieno, Seth Owusu-Agyei, Aoife Pauley, David Poland, Nahya Salim, Barbara Savarese, Jahit Sacarlal, David Schellenberg, Laurence Slutsker, Marcel Tanner, Johan Vekemans.

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The Independent Data Monitoring Committee: Malcolm Molyneux (Chair), Kate O'Brien, Kojo Kwadwo Koram.

The Local Safety Monitors: Pietra Virginio, Karim Manji, Gyikua Plange-Rhule, Samuel Newton, Paul Mitei, James A. Berkley, Grace Malenga, Juliana Otieno.

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Those listed below by study center who contributed in various ways to the trial:

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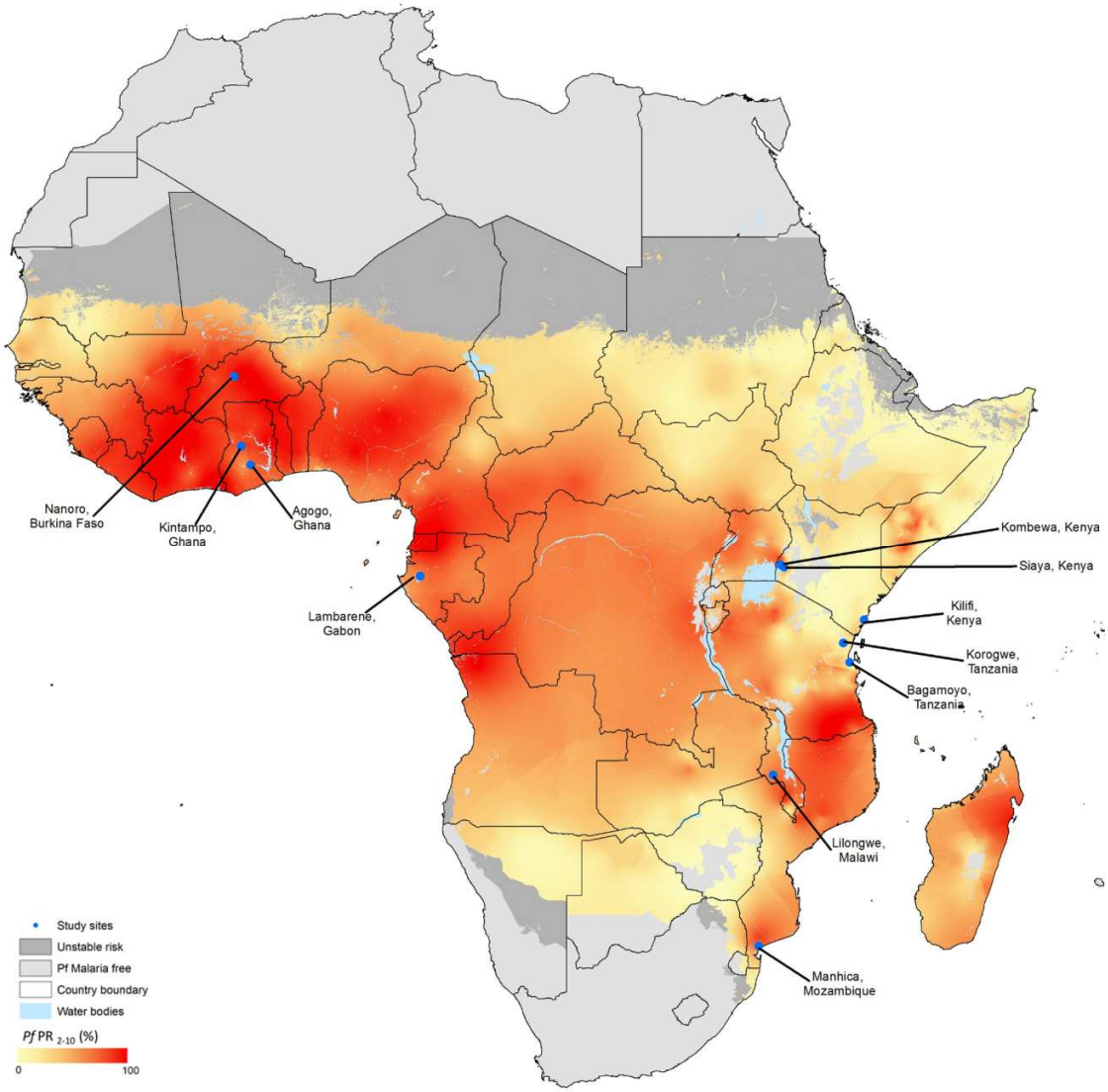
6. Supplementary figures and tables

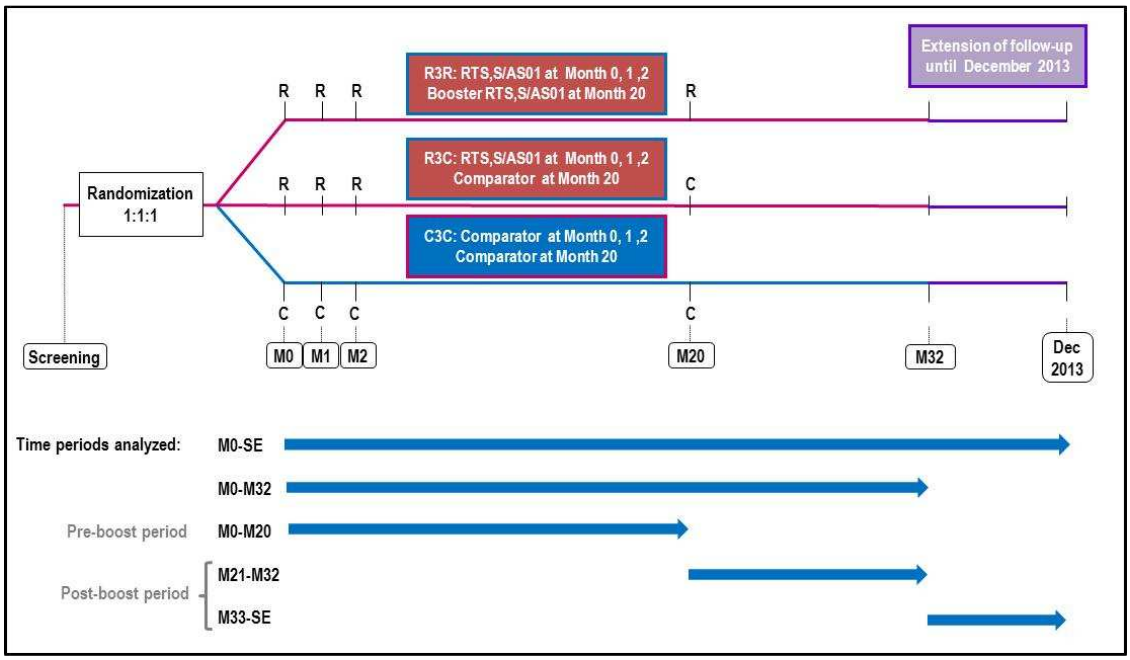
Figure S1. Study sites and malaria endemicity.



Adapted from Hay SI, Guerra CA, Gething, PW et al. A world malaria map: Plasmodium falciparum endemicity in 2007. *PLoS Med* 2009; 6(3): e1000048.

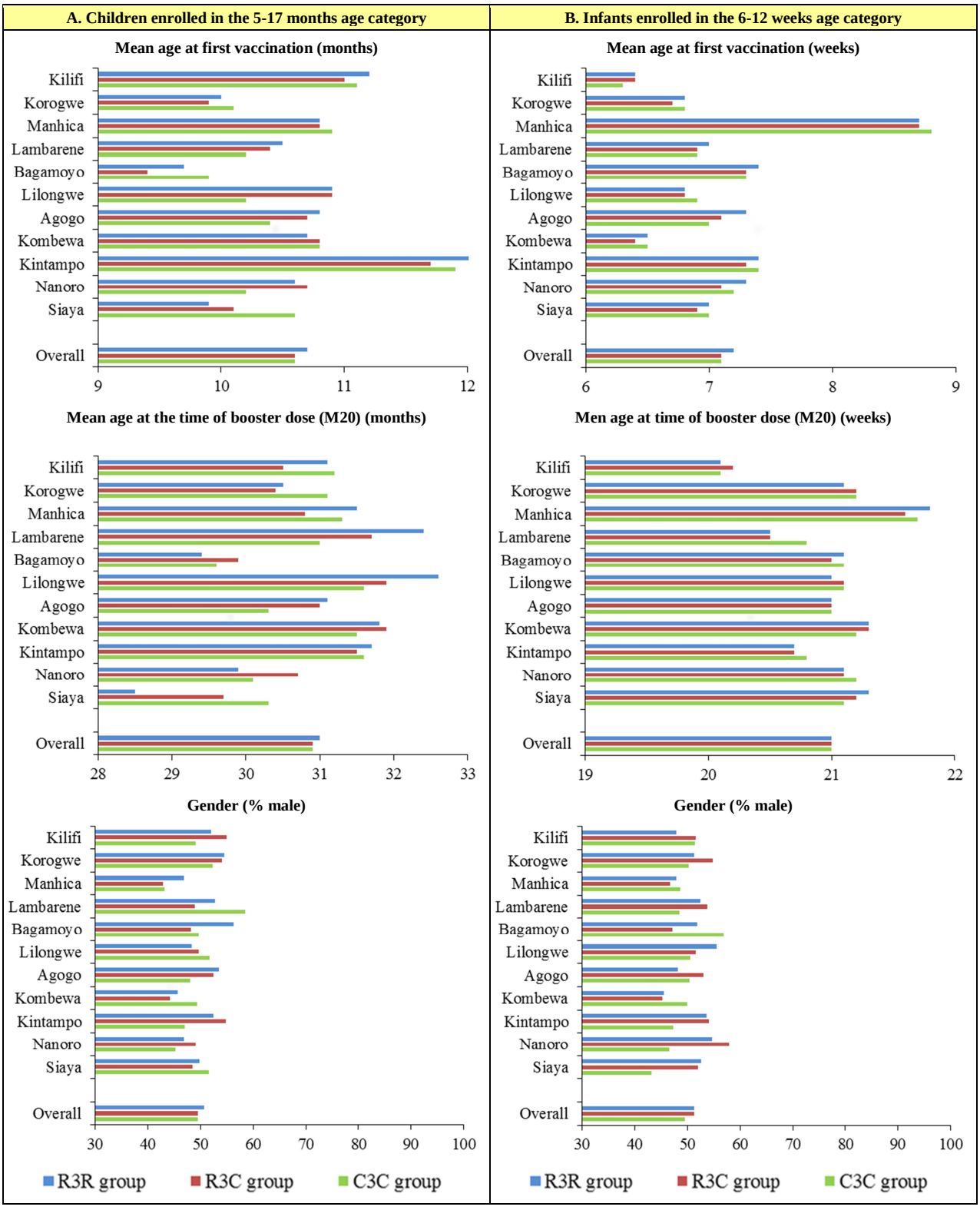
The location of each participating study site is shown on this previously published map showing the spatial distribution of *P. falciparum* malaria endemicity. The data are the model-based geostatistical point estimates of the annual mean *P. falciparum* parasite rate age-standardized for 2-10 years for 2007 within the stable spatial limits of *P. falciparum* malaria transmission, displayed as a continuum of yellow to red from 0%–100% (see map legend). The rest of the land area was defined as unstable risk (medium grey areas) or no risk (light grey). Nanoro, Burkina Faso has highly seasonal malaria transmission.

Figure S2. Overall study design.



M = study month; SE = study end. The study was extended until end of December 2013. The total follow-up time of participants varied depending on their enrolment date. The median follow-up time post dose 1 in the 6-12 weeks was R3R=37·8 months; R3C=37·7 months; C3C=37·8 months (median overall: 38 months). The median follow-up time post dose 1 in the 5-17 months was R3R=48·1 months; R3C=48·1 months; C3C=48·4 months (median overall: 48 months).

Figure S3. Baseline characteristics in each study site (intention-to-treat population).



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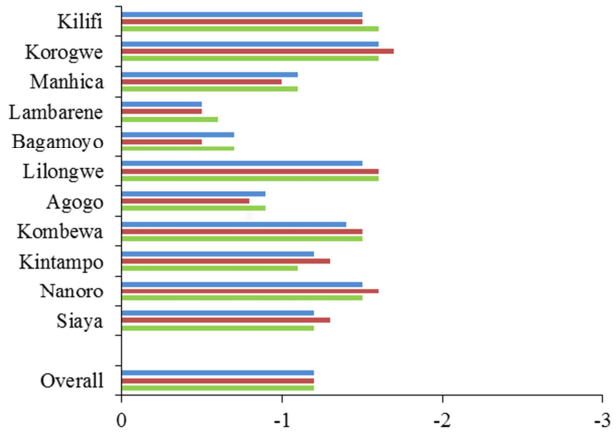
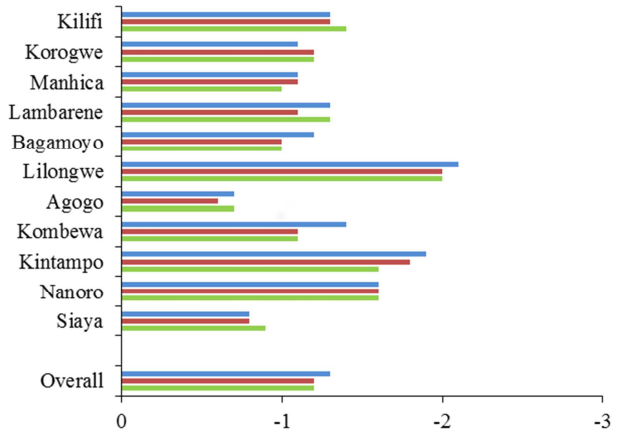
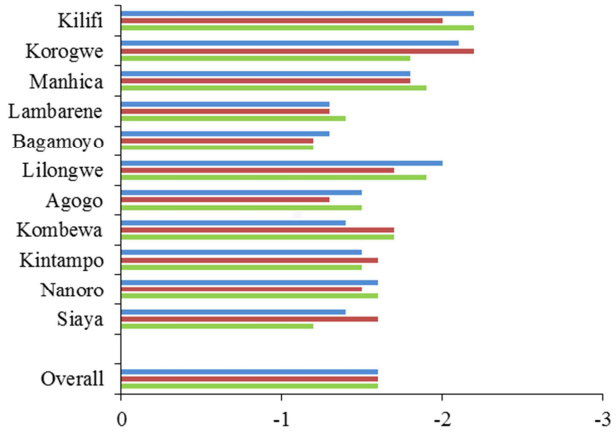
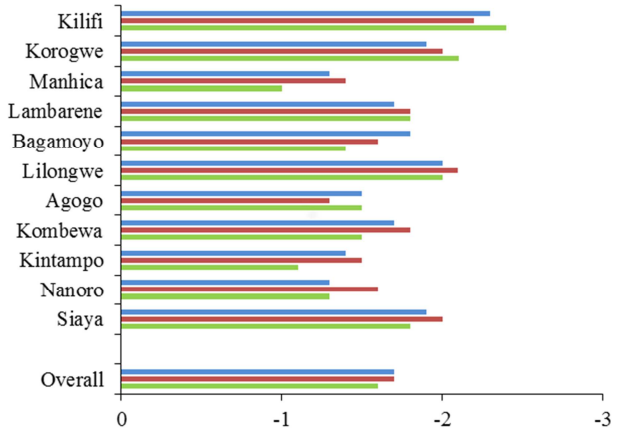
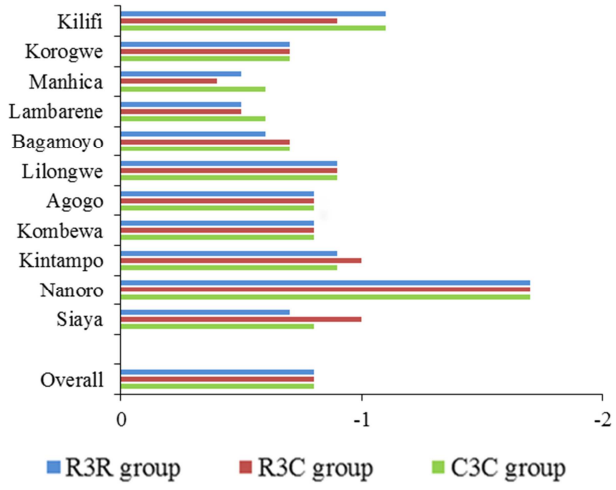
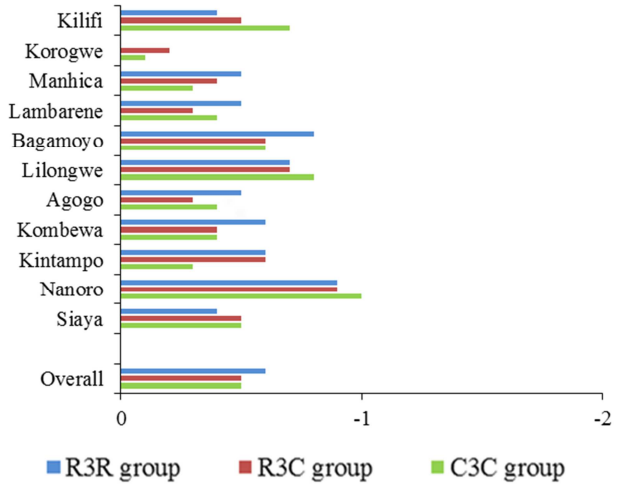
A. Children enrolled in the 5-17 months age category	B. Infants enrolled in the 6-12 weeks age category
Mean height-for-age Z-score at first vaccination	**Mean height-for-age Z-score at first vaccination**
	
Mean height-for-age Z-score at the time of booster dose (M20)	**Mean height-for-age Z-score at the time of booster dose (M20)**
	
Mean weight-for-age Z-score at first vaccination	**Mean weight-for-age Z-score at first vaccination**
	

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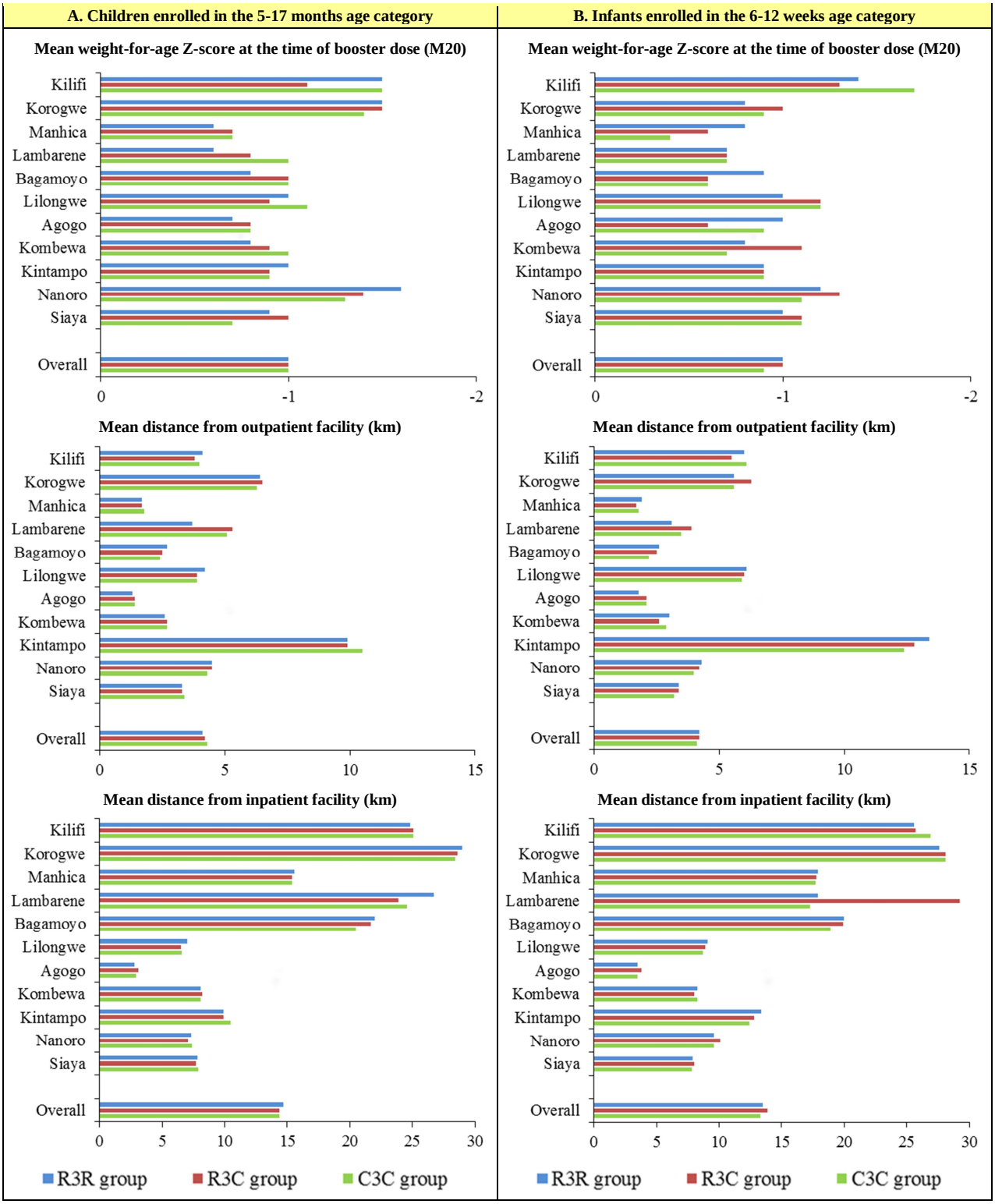

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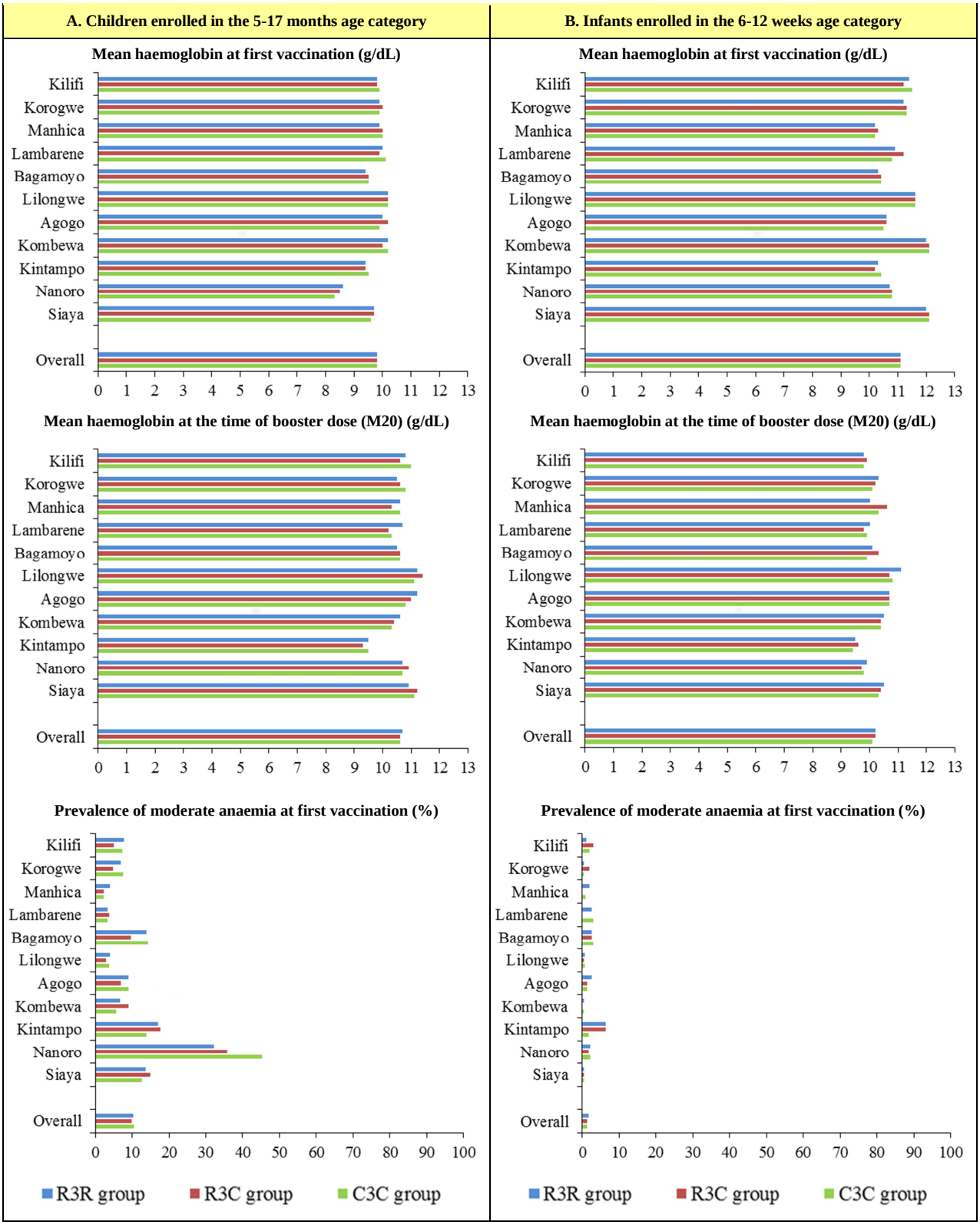

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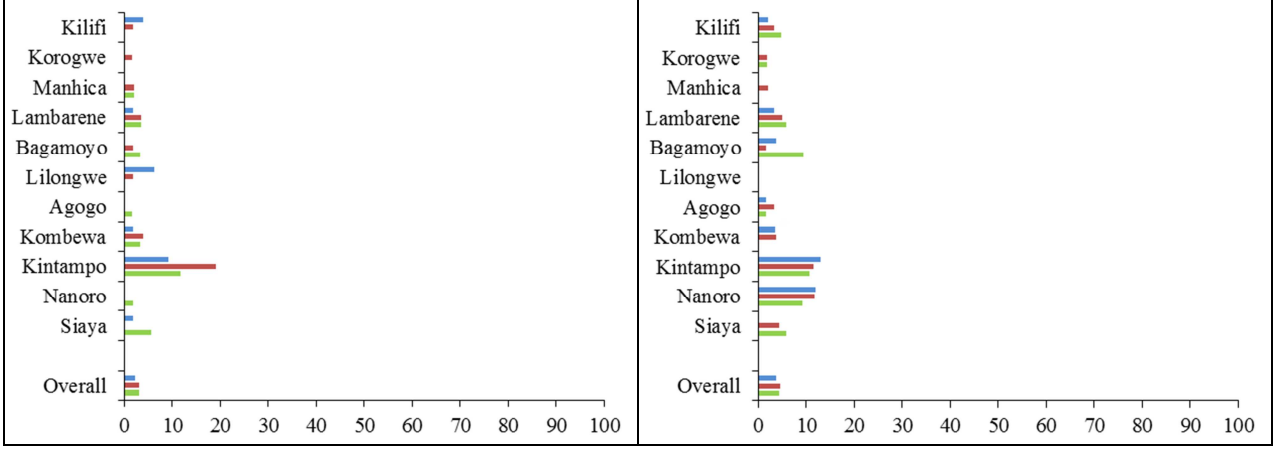
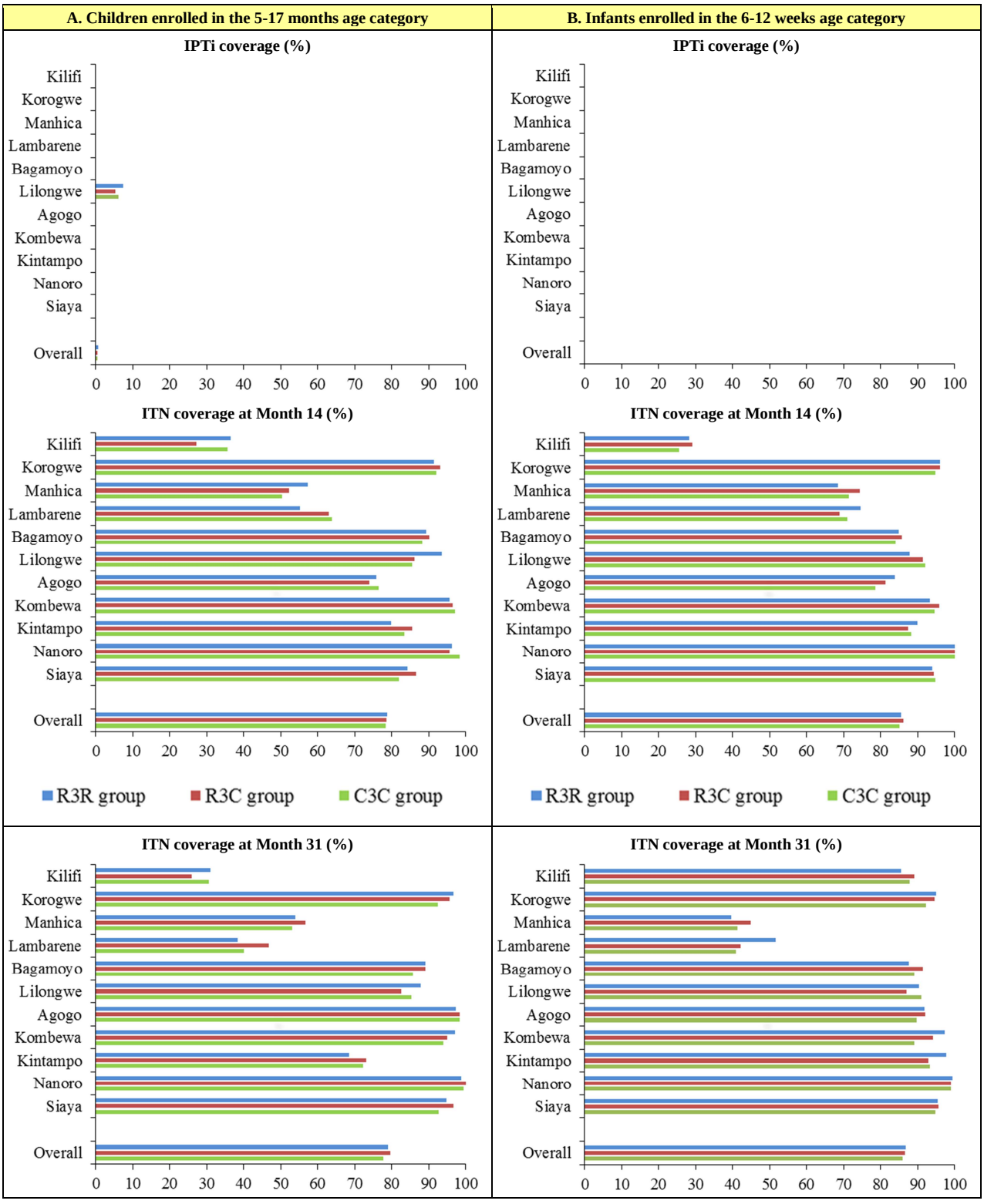
A. Children enrolled in the 5-17 months age category	B. Infants enrolled in the 6-12 weeks age category
Prevalence of moderate anaemia at the time of booster dose (M20) (%)	Prevalence of moderate anaemia at the time of booster dose (M20) (%)



Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria, defined as a measured or reported fever within previous 24h and parasite density >0 parasites per cubic millimetre (i.e. clinical malaria secondary case definition), measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up.
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
M20 = Month 20.
Moderate anaemia = a documented haemoglobin concentration < 8·0 g per decilitre identified at a cross sectional survey.

Figure S4. Malaria control measures in place at each study site (intention-to-treat population).



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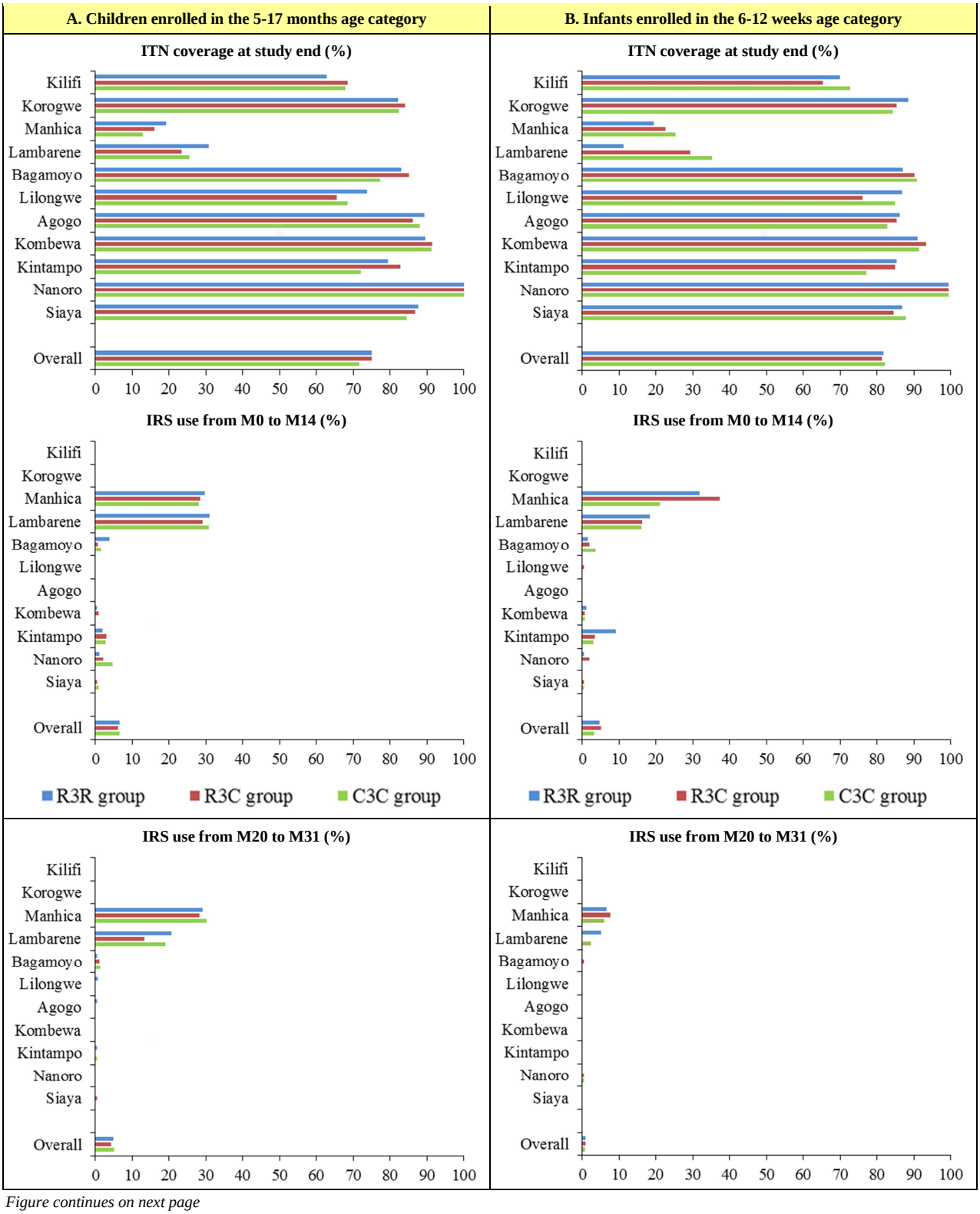

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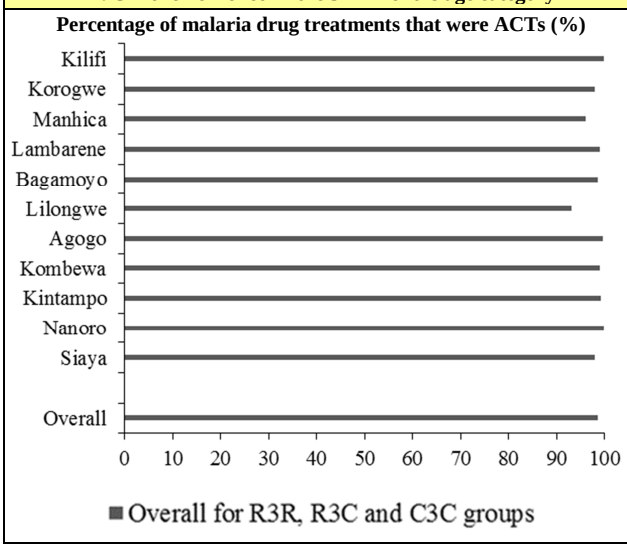
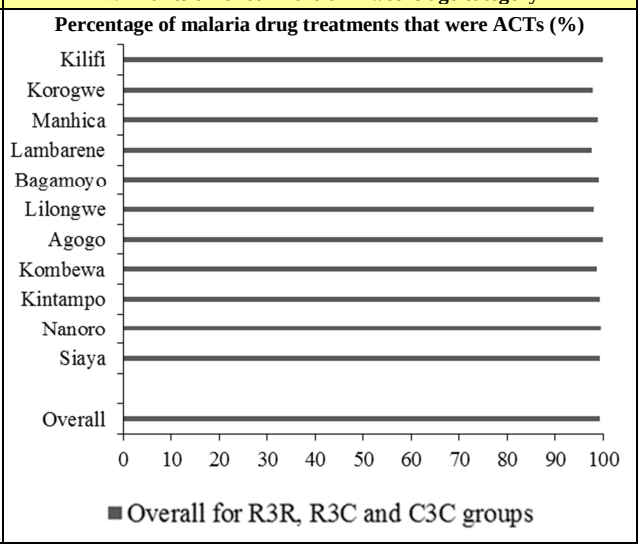
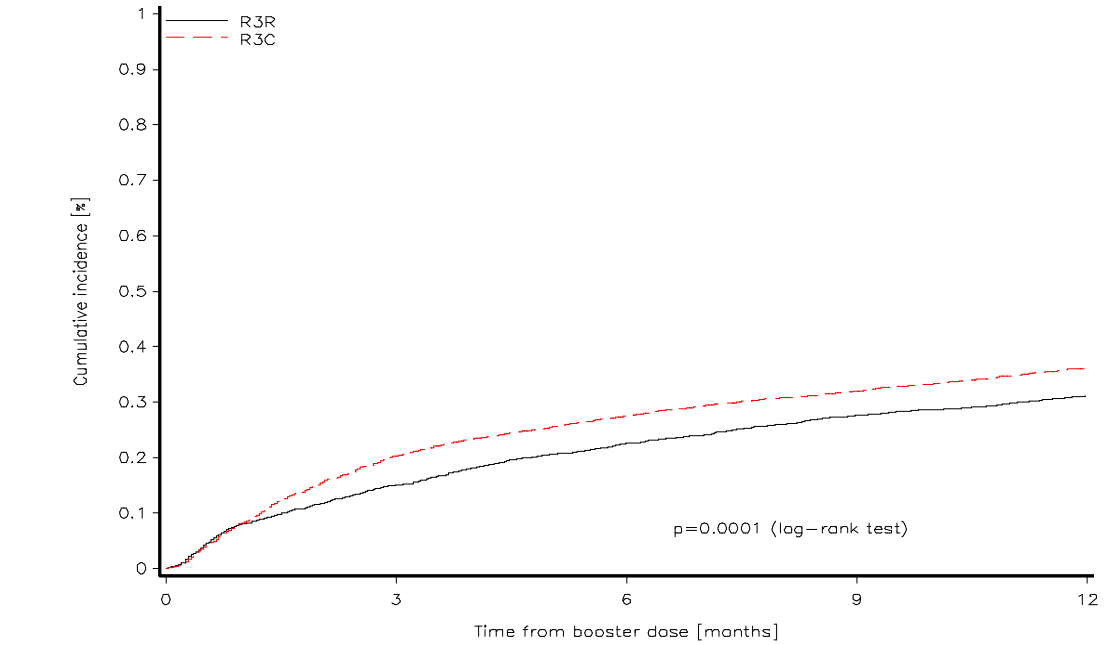
A. Children enrolled in the 5-17 months age category	B. Infants enrolled in the 6-12 weeks age category
	

Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria, defined as a measured or reported fever within previous 24h and parasite density >0 parasites per cubic millimetre (i.e. clinical malaria secondary case definition), measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up.
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
M20 = Month 20.
IPTi = intermittent preventive treatment of malaria in infants: percentage of subjects with at least one application from study start until end of follow-up period.
ITN = insecticide treated bed-net with or without holes.
IRS = indoor residual spraying.
ACT = artemisinin-based combination therapy.

Figure S5. Cumulative incidence of clinical malaria from booster dose until Month 32 among children in the 5-17 months age category (intention-to-treat population).



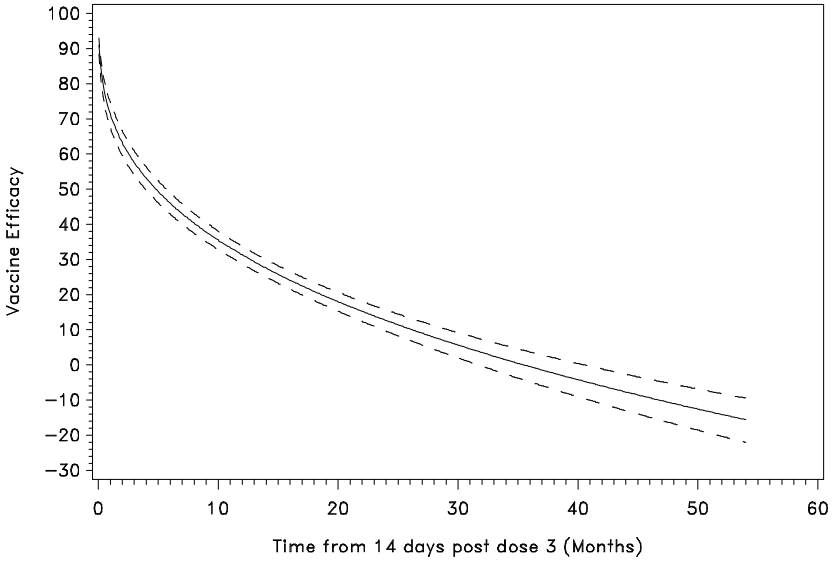
Number at risk

R3R	2679	2230	2011	1844	1511
R3C	2717	2130	1909	1766	1411

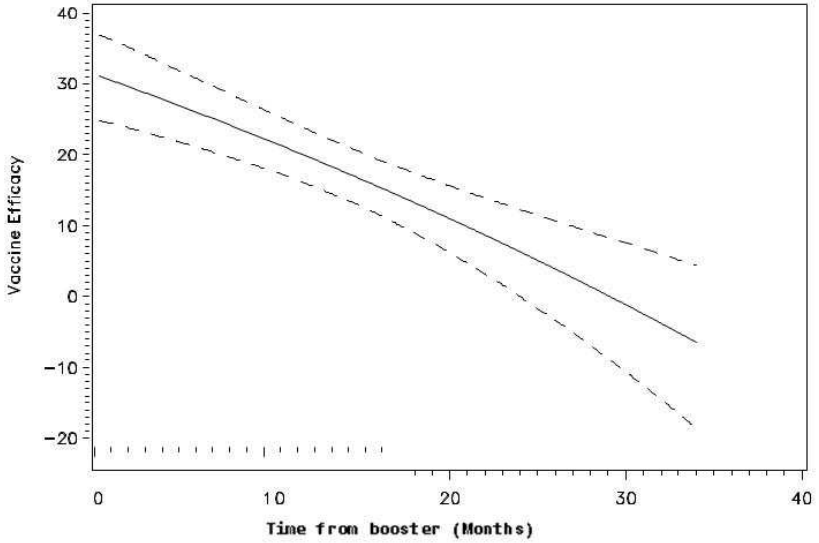
The graph shows the cumulative incidence of first or only episode of clinical malaria (primary case definition) over the 12 months period following the booster dose (i.e. until Month 32).
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.

Figure S6. Vaccine efficacy over time (clinical malaria primary case definition) in the 5-17 months age category (per-protocol population).

A. VE over time in the R3C group : all episodes of clinical malaria primary case definition (model=group*(log(time))) (M2.5-SE)

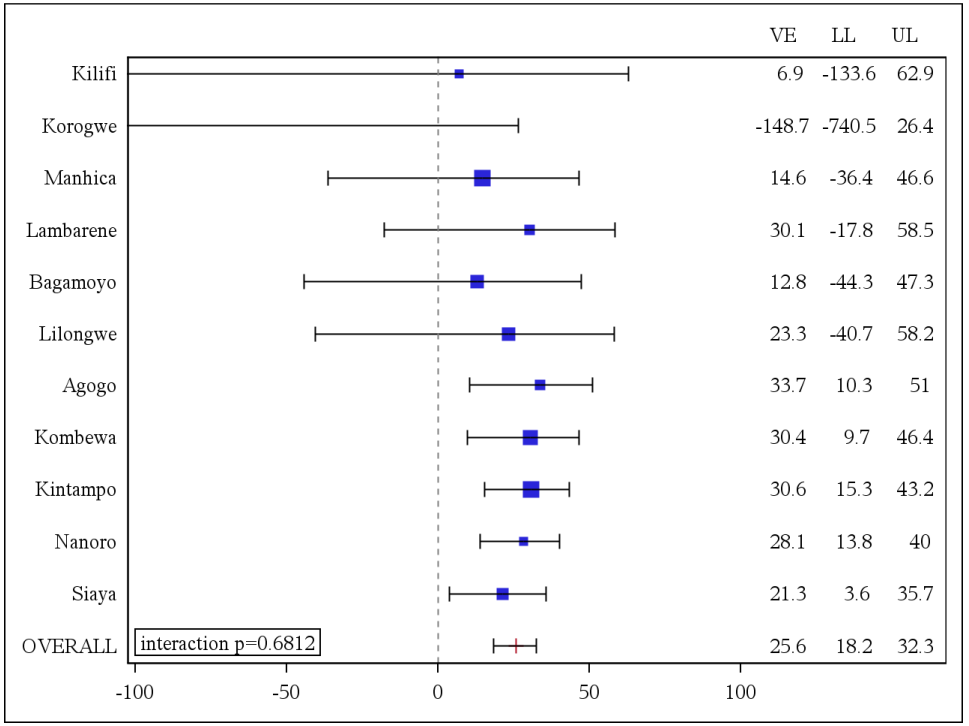


B. VE over time post booster dose in the R3R group : all episodes of clinical malaria primary case definition (model=group*(time)) (M21-SE)



Cox regression models including all episodes of clinical malaria (Andersen-Gill) with time-varying covariates (time, log(time), sqrt(time), time²..). The best model fit was selected based on AIC and SBC and plotted VE over time using the selected model.
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
M2·5-SE = follow-up from 14 days post dose 3 (Month 2·5) to study end (end of extension phase).
M21-SE = follow-up from day of booster dose to study end (end of extension phase).

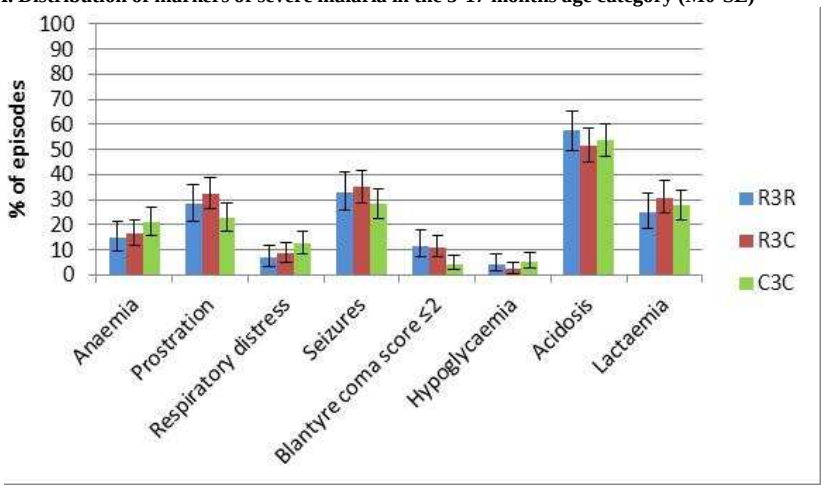
Figure S7. Incremental vaccine efficacy of a booster dose against clinical malaria by study site among children in the 5-17 months age category (intention-to-treat population).



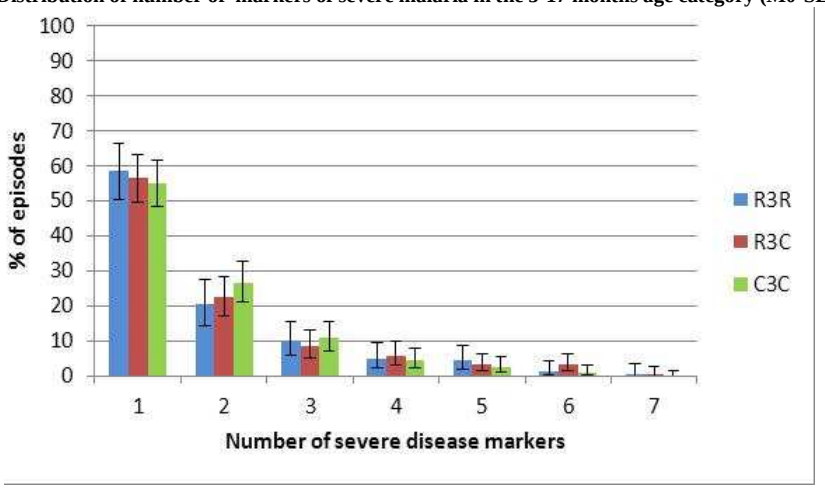
Incremental vaccine efficacy of a booster dose against all episodes of clinical (primary case definition) (M21-M32).
The size of each blue square reflects the relative number of subjects enrolled at each study site; the horizontal bars show the lower limit and upper limit of the 95% confidence interval. Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria, defined as a measured or reported fever within previous 24h and parasite density >0 parasites per cubic millimetre (i.e. clinical malaria secondary case definition), measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up.
M21-M32 = follow-up from day of booster dose to 32 months post dose 1 (Month 32).
VE = vaccine efficacy against all episodes of clinical malaria meeting the primary case definition unadjusted for covariates.
LL = lower limit of the 95% confidence interval.
UL = upper limit of the 95% confidence interval.

Figure S8. Markers of severe malaria in children and young infants by vaccination group (intention-to-treat population).

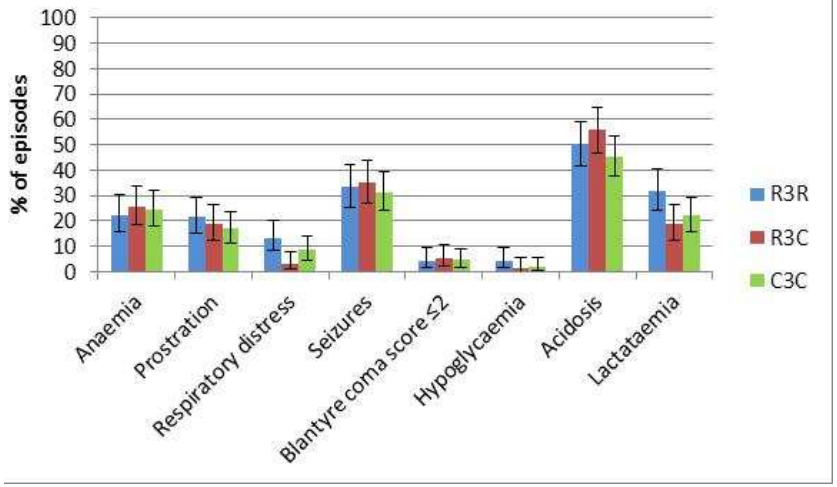
A. Distribution of markers of severe malaria in the 5-17 months age category (M0-SE)



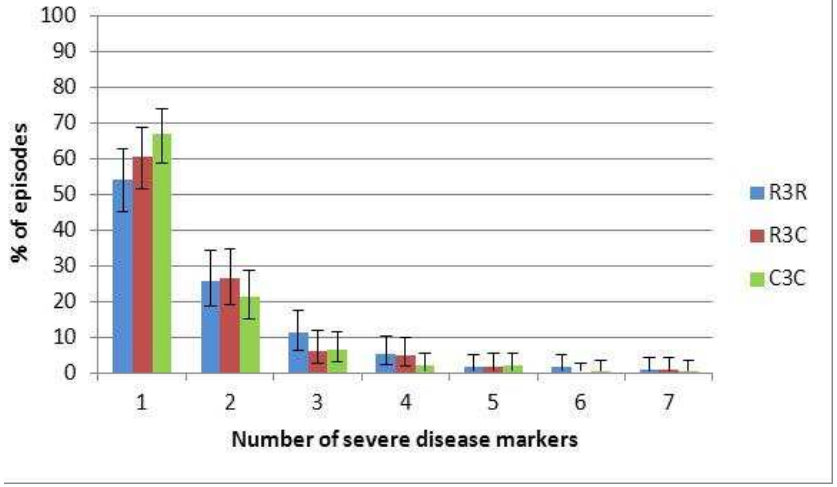
B. Distribution of number of markers of severe malaria in the 5-17 months age category (M0-SE)



C. Distribution of markers of severe malaria in the 6-12 weeks age category(M0-SE)

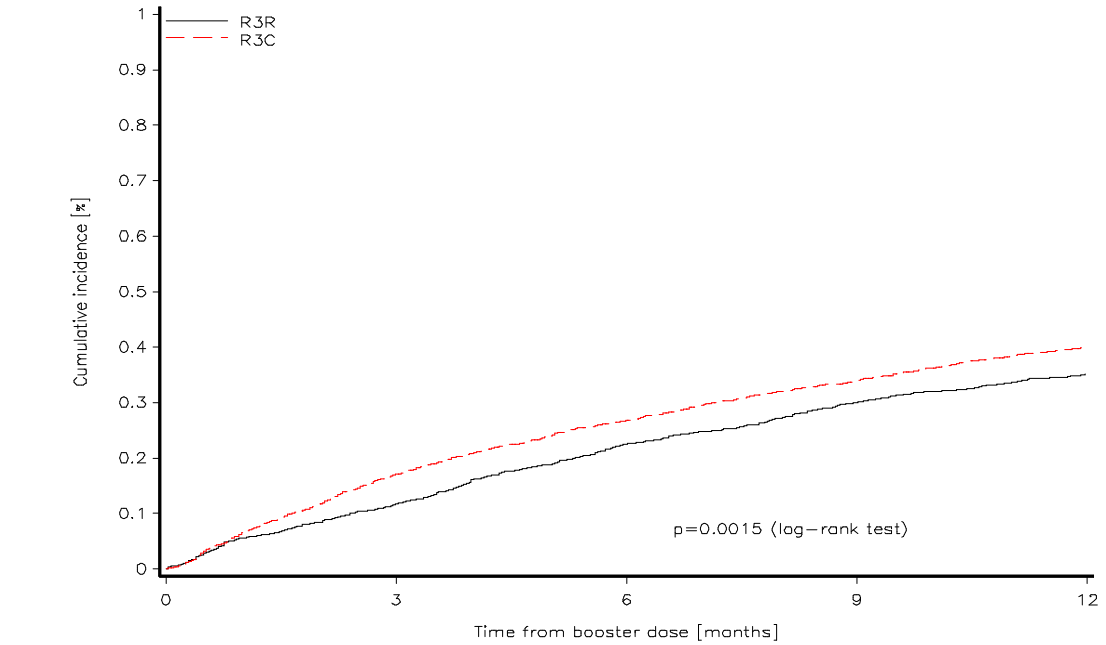


D. Distribution of number of markers of severe malaria in the 6-12 weeks age category (M0-SE)



Analysis of episodes of severe malaria meeting the secondary case definition.
Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2, two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin concentration of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
Error bars represent 95% confidence interval.
% of episodes = proportion of the total number of severe malaria cases per group.
Anaemia= haemoglobin < 50 g/L.
Prostration = in an acutely sick child, the inability to perform previously-acquired motor function: in a child previously able to stand, inability to stand; in a child previously able to sit, inability to sit and in a very young child, inability to suck.
Respiratory distress = lower chest wall indrawing or abnormally deep breathing.
Seizures = two or more seizures occurring in the total time period including 24 hours prior to admission time in the emergency room and during hospitalization.
Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness).
Hypoglycaemia = glucose < 2·2 mmol/L.
Acidosis = base excess ≤ -10·0 mmol/L.
Lactaemia = lactate ≥ 5·0 mmol/L.

Figure S9. Cumulative incidence of clinical malaria from booster dose until Month 32 among infants in the 6-12 weeks age category (intention-to-treat population).



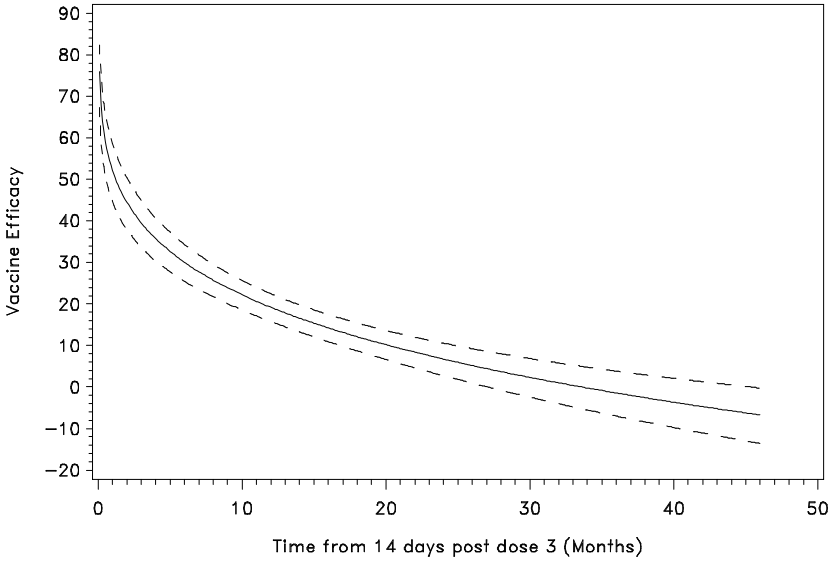
Number at risk

R3R	1966	1706	1481	1320	1084
R3C	1995	1617	1410	1258	1033

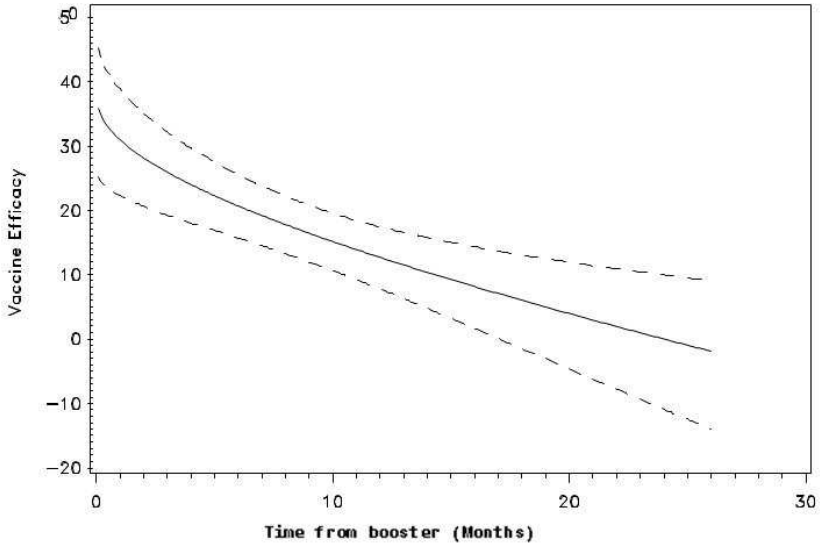
The graph shows the cumulative incidence of first or only episode of clinical malaria primary case definition over the 12 months period following the booster dose (i.e. until Month 32).
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.

Figure S10. Vaccine efficacy over time (clinical malaria primary case definition) in the 6-12 weeks age category (per-protocol population).

A. VE over time in the R3C group : all episodes of clinical malaria primary case definition (model=group*(log(time))) (M2.5-SE)

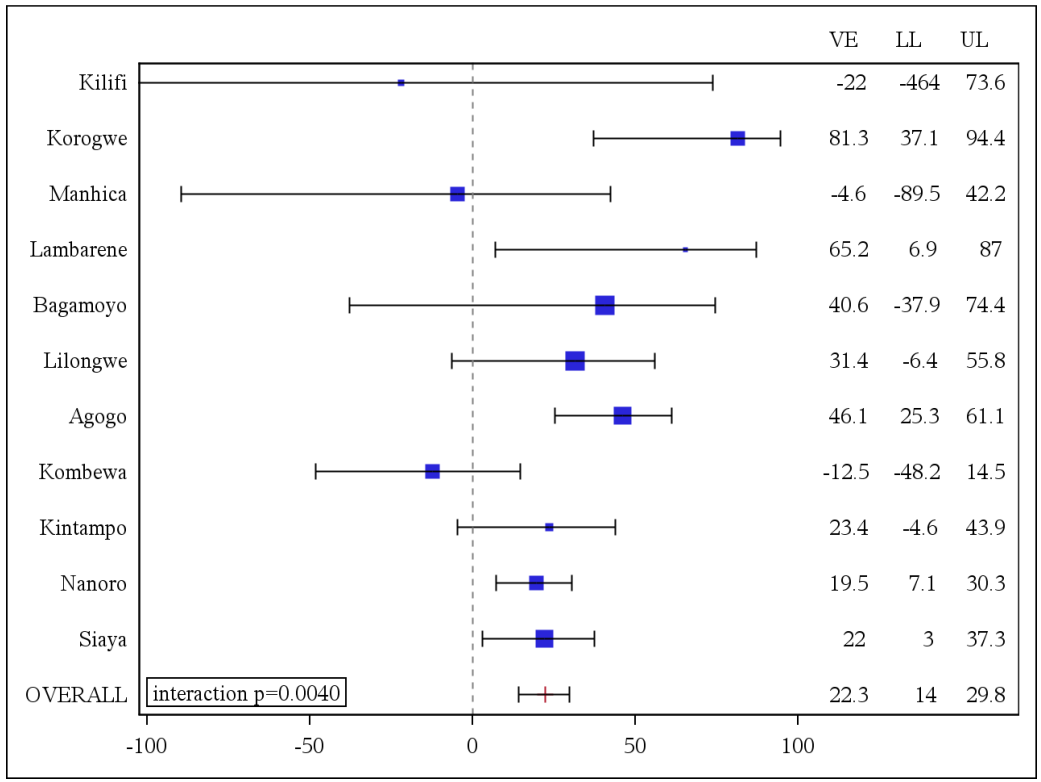


B. VE over time post booster dose in the R3R group : all episodes of clinical malaria primary case definition (model=group*(SQRT(time))) (M21-SE)



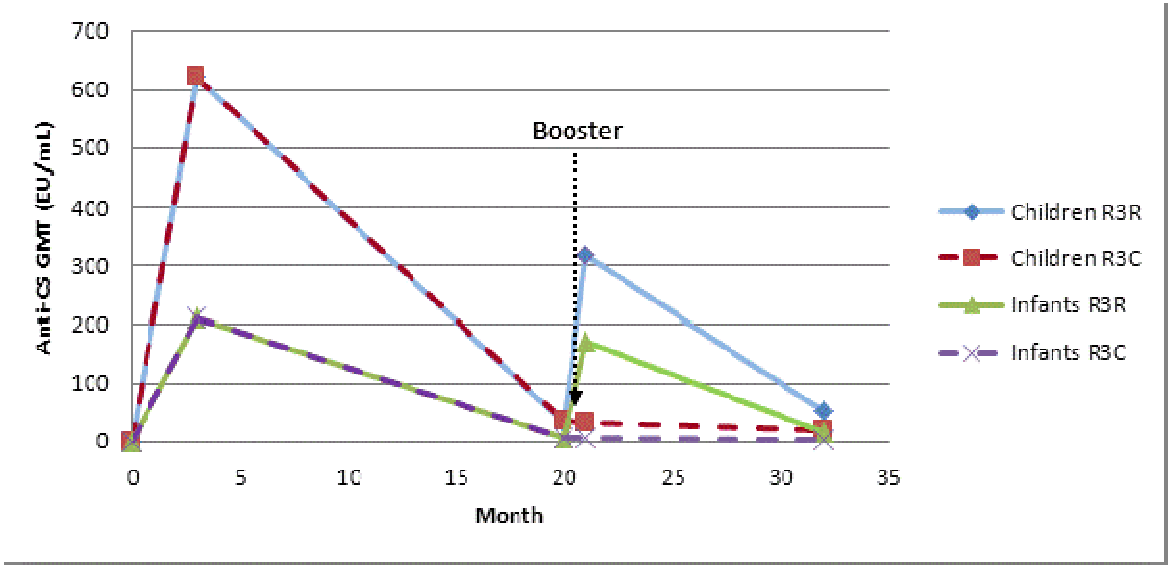
Cox regression models including all episodes of clinical malaria (Andersen-Gill) with time-varying covariates (time, log(time), sqrt(time), time²..). The best model fit was selected based on AIC and SBC and plotted VE over time using the selected model.
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
M2·5-SE = follow-up from 14 days post dose 3 (Month 2·5) to study end (end of extension phase).
M21-SE = follow-up from day of booster dose to study end (end of extension phase).

Figure S11. Incremental vaccine efficacy of a booster dose against clinical malaria by study site among infants in the 6-12 weeks age category (intention-to-treat).



Incremental vaccine efficacy of a booster dose against all episodes of clinical (primary case definition) (M21-M32).
The size of each blue square reflects the relative number of subjects enrolled at each study site; the horizontal bars show the lower limit and upper limit of the 95% confidence interval. Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria, defined as a measured or reported fever within previous 24h and parasite density >0 parasites per cubic millimetre (i.e. clinical malaria secondary case definition), measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up.
M21-M32 = follow-up from day of booster dose to 32 months post dose 1 (Month 32).
VE = vaccine efficacy against all episodes of clinical malaria meeting the primary case definition unadjusted for covariates.
LL = lower limit of the 95% confidence interval.
UL = upper limit of the 95% confidence interval.

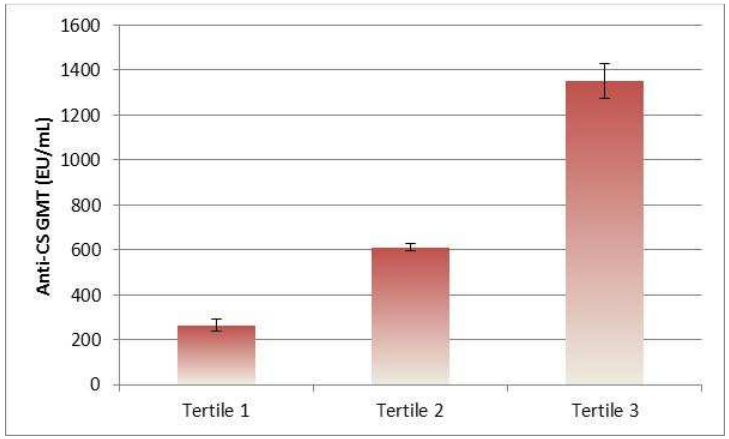
Figure S12. Anti-CS geometric mean titres in each age category (per-protocol population for immunogenicity).



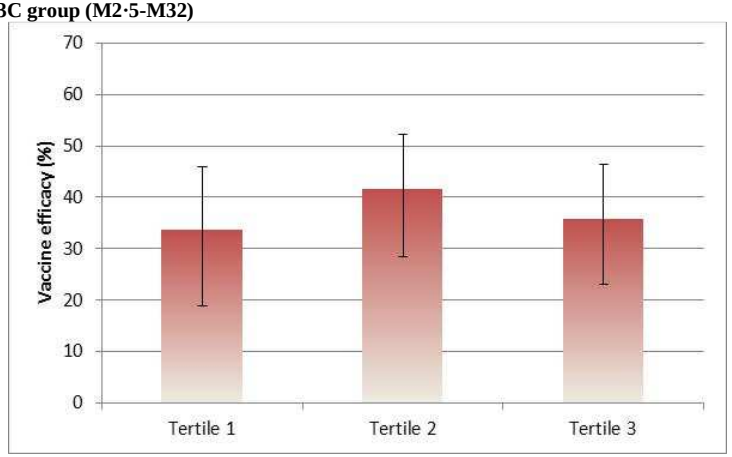
R3R+R3C = RTS,S/AS01 primary schedule (combined R3R + R3C groups analysed over the period before the administration of the booster dose at Month 20). R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
Anti-CS = anti-circumsporozoite protein antibodies.
GMT = geometric mean antibody titre calculated on all subjects.
EU/mL = ELISA unit per millilitre.

Figure S13. Vaccine efficacy by tertile of anti-CS antibody concentration among children in the 5-17 months age category (per-protocol population for efficacy).

A. Anti-CS geometric mean titres at one month post dose 3 in the R3C group

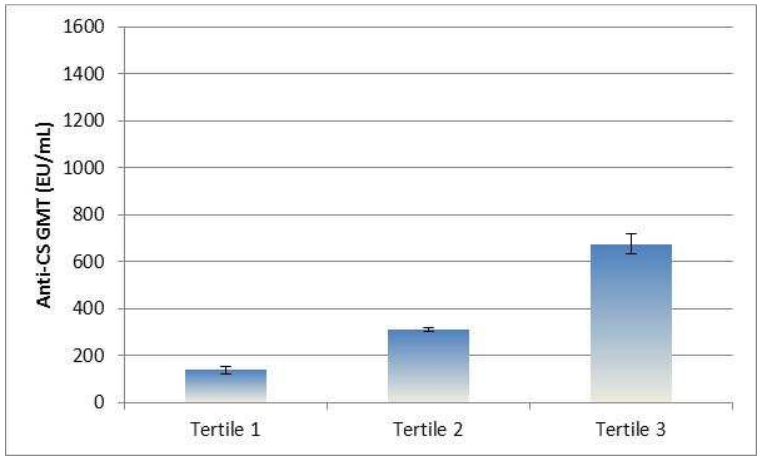


B. Vaccine efficacy against clinical malaria per anti-CS tertile over 30 months post dose 3 in the R3C group (M2·5-M32)

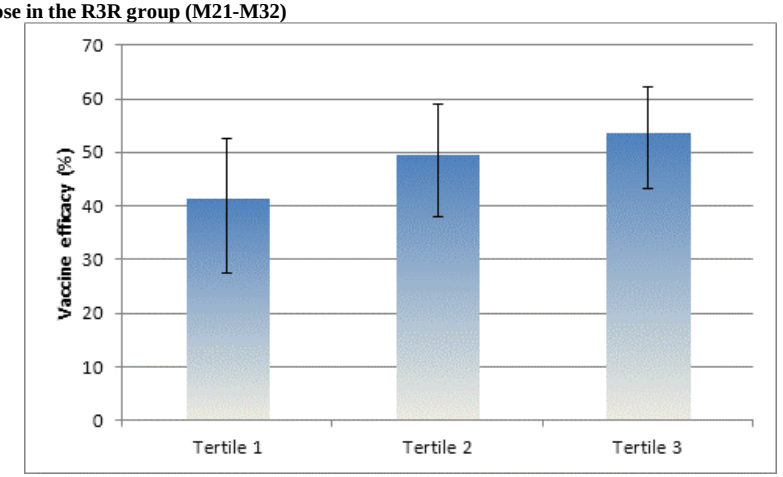


Tertile 3 vs. tertile 1: 3·6% (-25·6;26·0) reduction in malaria episodes (p=0·7865)

C. Anti-CS geometric mean titres at one month post booster dose in the R3R group



D. Vaccine efficacy against clinical malaria per anti-CS tertile over 12 months post booster dose in the R3R group (M21-M32)

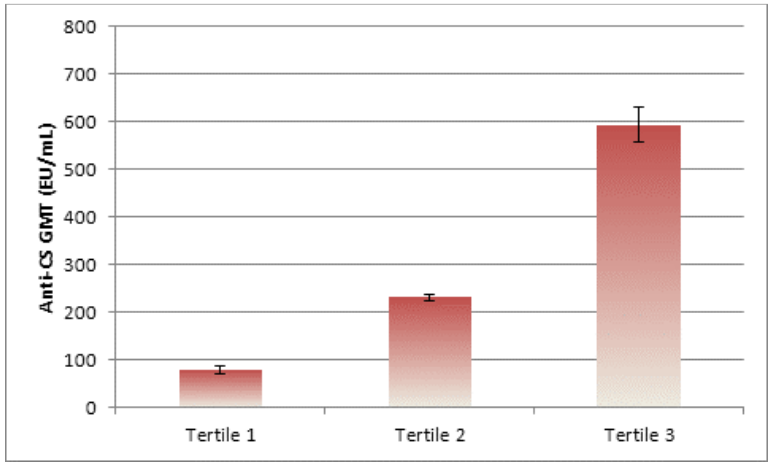


Tertile 3 vs. tertile 1: 23·2% (-4·1;43·3) reduction in malaria episodes (p=0·0888)

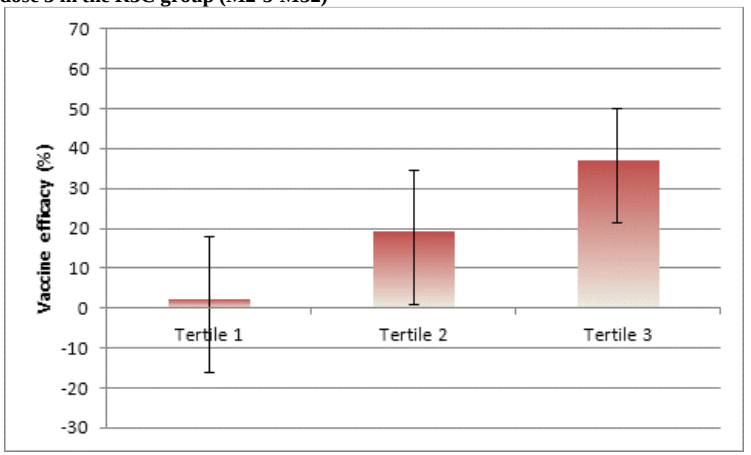
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
Error bars represent 95% confidence interval.
Anti-CS = anti-circumsporozoite protein antibodies.
GMT = geometric mean antibody titre.
EU/mL = ELISA unit per millilitre.
M21-M32 = follow-up from day of booster dose to 30 months post dose 3 (Month 32).
M2·5-M32 = follow-up from 14 days post dose 3 (Month 2·5) to 30 months post dose 3 (Month 32).
P-value from negative binomial random effect model.

Figure S14. Vaccine efficacy by tertile of anti-CS antibody concentration among infants in the 6-12 weeks age category (per-protocol population for efficacy).

A. Anti-CS geometric mean titres at one month post dose 3 in the R3C group

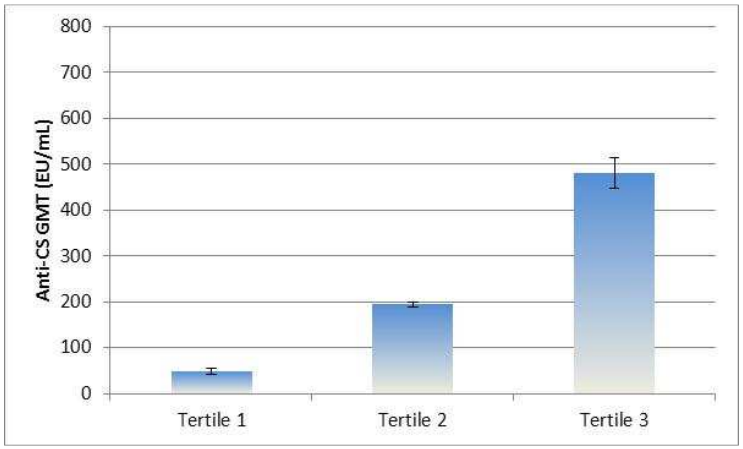


B. Vaccine efficacy against clinical malaria per anti-CS tertile over 30 months post dose 3 in the R3C group (M2·5-M32)

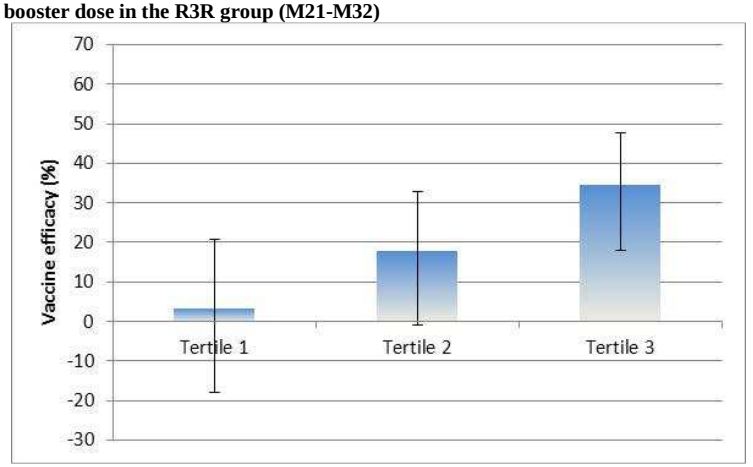


Tertile 3 vs. tertile 1: 36·9% (17·3;51·8) reduction in malaria episodes (p=0·0009)

C. Anti-CS geometric mean titres at one month post booster dose in the R3R group



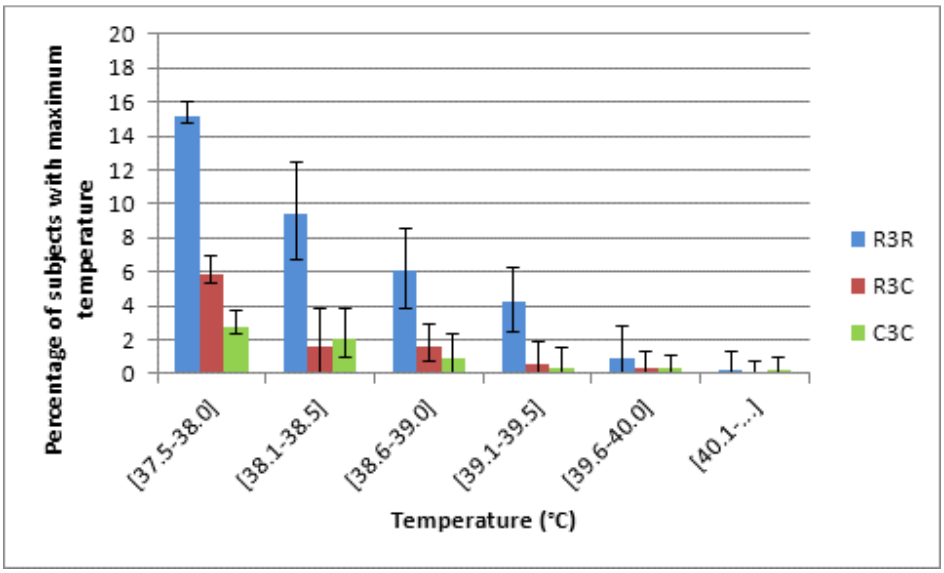
D. Vaccine efficacy against clinical malaria per anti-CS tertile over 12 months post booster dose in the R3R group (M21-M32)



Tertile 3 vs. tertile 1: 34·3% (10·8; 51·6) reduction in malaria episodes (p=0·0072)

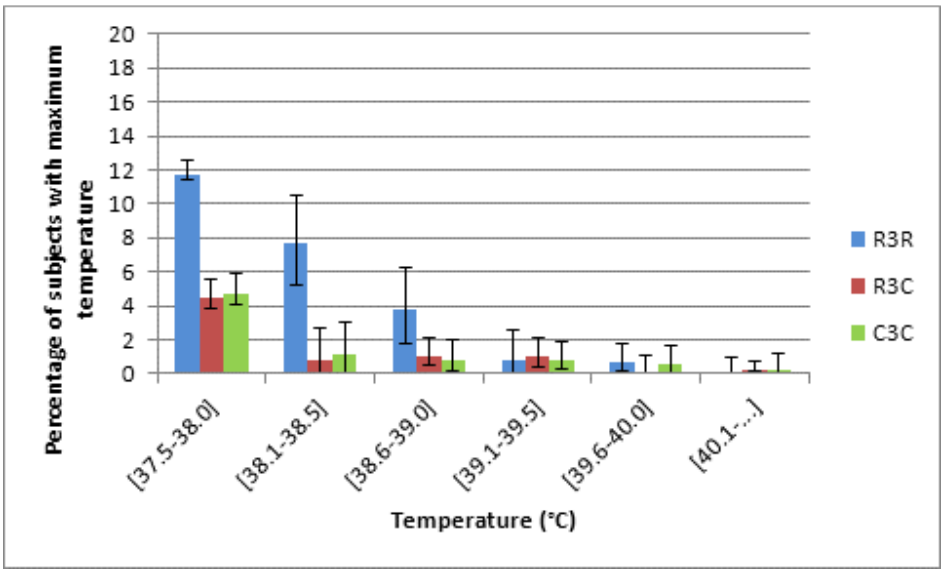
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
Error bars represent 95% confidence interval.
Anti-CS = anti-circumsporozoite protein antibodies.
GMT = geometric mean antibody titre.
EU/mL = ELISA unit per millilitre.
M21-M32 = follow-up from day of booster dose to 30 months post dose 3 (Month 32).
M2·5-M32 = follow-up from 14 days post dose 3 (Month 2·5) to 30 months post dose 3 (Month 32).
P-value from negative binomial random effect model.

Figure S15. Distribution of maximal temperature within seven days post booster dose among children in the 5-17 months age category (intention-to-treat population).



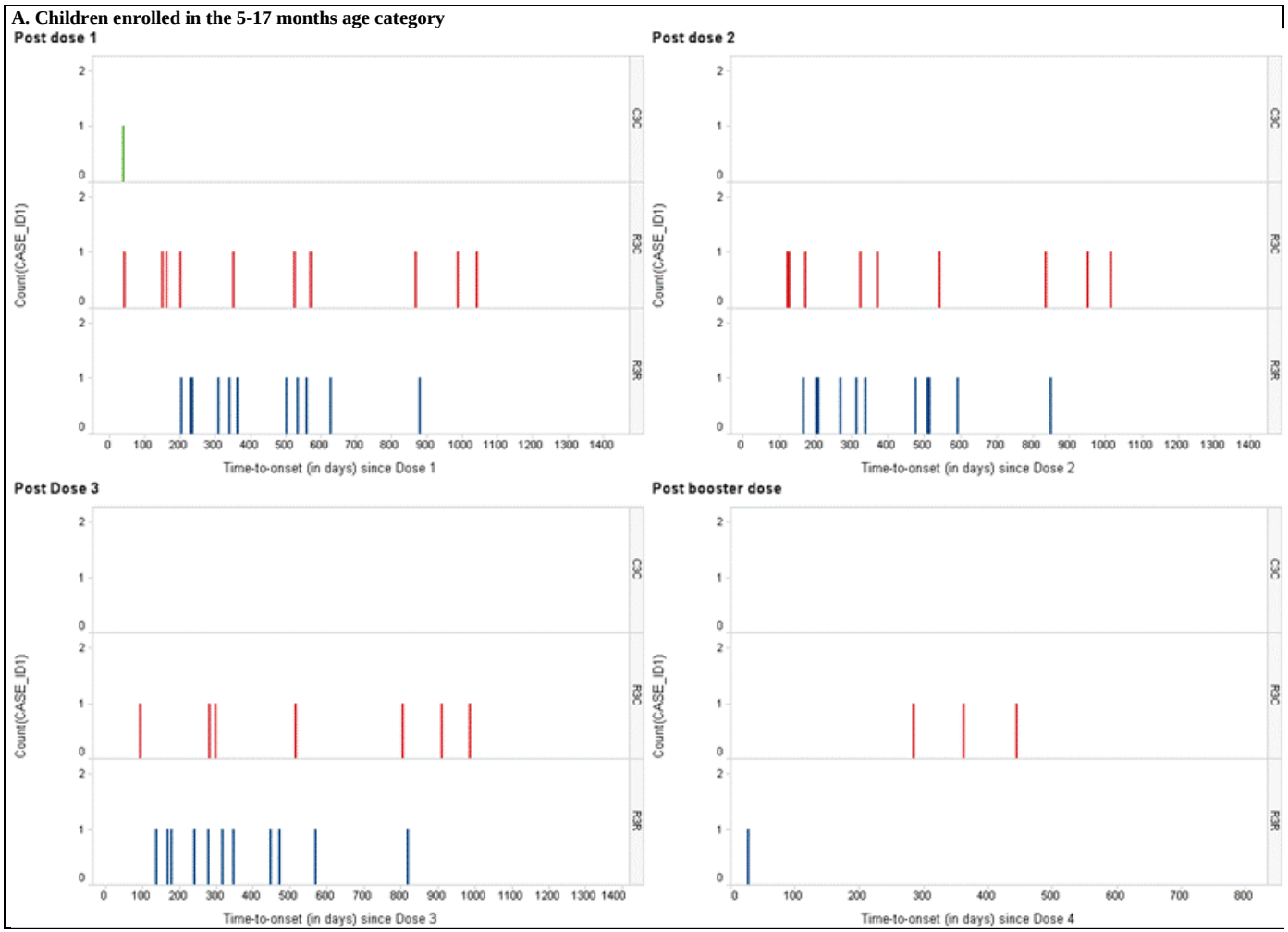
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
Error bars represent 95% confidence interval.

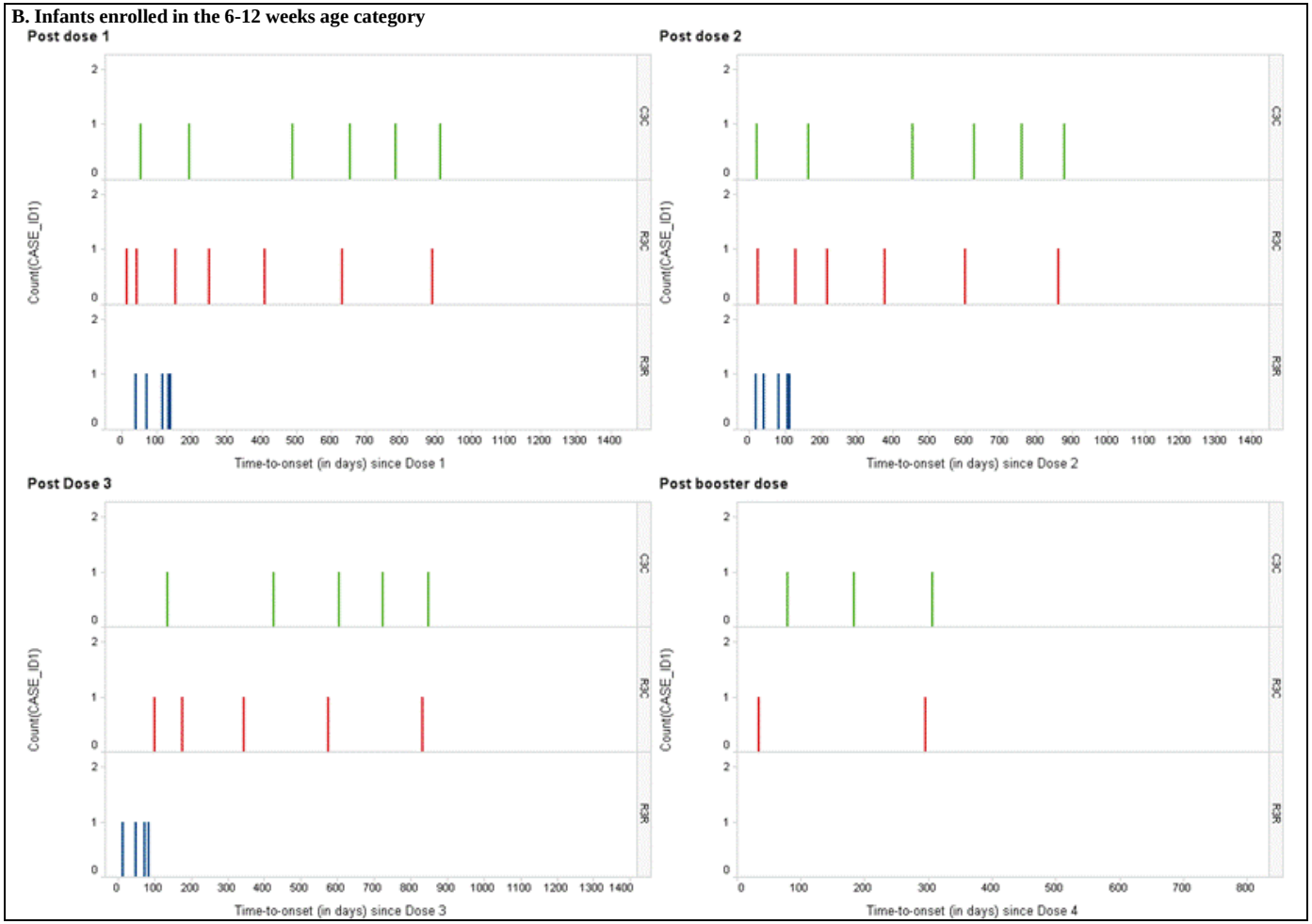
Figure S16. Distribution of maximal temperature within seven days post booster dose among infants in the 6-12 weeks age category (intention-to-treat population).



R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
Error bars represent 95% confidence interval.

Figure S17. Time-to-onset distribution of meningitis cases post dose 1, dose 2, dose 3 and booster dose for both age categories (intention-to-treat population).





R3R = RTS,S/AS01 primary schedule with booster (Blue bars).
R3C = RTS,S/AS01 primary schedule without booster (Red bars).
C3C = control group (Green bars).
MedDRA Preferred Term = Meningitis, Meningitis haemophilus, Meningitis meningococcal, Meningitis pneumococcal, Meningitis salmonella, Meningitis tuberculous, Meningitis viral.

Table S1a. List of ethic committees and review boards.

Study centres	Ethics review body
Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso	Western Institutional Review Board (WIRB)
	Comité d'Ethique Institutionnel du Centre Muraz (Institutional Ethics Committee of Muraz Centre)
	Comite d'Ethique pour la Recherche en Santé (Ethics Committee for Health Research)
Albert Schweitzer Hospital, Lambaréné, Gabon	Western Institutional Review Board (WIRB)
	Comité d'Ethique Régional Indépendant de Lambaréné (CERIL) (Independent Regional Ethics Committee of Lambaréné)
	Comité National d'Ethique pour la Recherche (National Ethics Committee for Research The Board)
School of Medical Sciences, Kumasi (Agogo), Ghana	Western Institutional Review Board (WIRB)
	Ghana Health Service (GHS) Ethical Review Committee (ERC) Research and Development Division
	Committee on Human Research Publication and Ethics (CHRPE)
Kintampo Health Research Centre, Kintampo, Ghana	Western Institutional Review Board (WIRB)
	Kintampo Health Research Centre (KHRC) Institutional Ethics Committee (IEC)
	London School of Hygiene and Tropical Medicine Research Ethics Committee
	Ghana Health Service (GHS) Ethical Review Committee (ERC) Research and Development Division
KEMRI - Walter Reed Project, Kombewa, Kenya	Western Institutional Review Board (WIRB)
	Kenya Medical Research Institute (KEMRI) National Ethics Review Committee
	Walter Reed Army Institute of Research (WRAIR) IRB
KEMRI - Wellcome Trust Research Program, Kilifi, Kenya	Western Institutional Review Board (WIRB)
	Kenya Medical Research Institute (KEMRI) National Ethics Review Committee
KEMRI/CDC Research and Public Health Collaboration, Siaya, Kenya	Western Institutional Review Board (WIRB)
	Kenya Medical Research Institute (KEMRI) National Ethics Review Committee
	Centres for Disease Control and Prevention (CDC) – IRB
University of North Carolina Project, Lilongwe, Malawi	Western Institutional Review Board (WIRB)
	National Health Sciences Research Committee
	Office of Human Research Ethics
Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique	Western Institutional Review Board (WIRB)
	Comitè Etic Investigació Clinica (Hospital Clinic (Barcelona University) Ethics Committee)
	Comité Nacional de Bioética para a Saúde (National Bioethical Health Committee, Mozambique)
Ifakara Health Institute, Bagamoyo, Tanzania	Western Institutional Review Board (WIRB)
	Tanzanian Medical Research Coordinating Committee (MRCC) operating within the National Institute for Medical Research (NIMR)
	Ethikkommission beider Basel (EKBB) (Ethics Committee of the local government responsible for the Swiss Tropical and public Health Institute and the University of Basel, Switzerland)
	Ifakara Health Institute IRB
National Institute for Medical Research, Korogwe, Tanzania	Western Institutional Review Board (WIRB)
	London School of Hygiene and Tropical Medicine Research Ethics Committee
	Tanzania Medical Research Coordinating Committee (MRCC) operating within National Institute for Medical Research (NIMR)
	The Danish National Committee on Biomedical Research Ethics

Table S1b. Investigational centres and affiliated partners.

Country	Investigational centres	Abbreviated name	Affiliated partner
Burkina Faso	Institut de Recherche en Science de la Santé	Nanoro	Prince Leopold Institute of Tropical Medicine, Belgium
Gabon	Albert Schweitzer Hospital, Medical Research Unit	Lambaréné	University of Tübingen, Germany
Ghana	Kwame Nkrumah University of Science and Technology, School of Medical Sciences, Kumasi	Agogo	
Ghana	Kintampo Health Research Centre	Kintampo	London School of Hygiene and Tropical Medicine, UK
Kenya	KEMRI - Wellcome Trust Research Program	Kilifi	University of Oxford, UK
Kenya	KEMRI - Walter Reed Project	Kombewa	Walter Reed Army Institute of Research, USA
Kenya	KEMRI/CDC Research and Public Health Collaboration	Siaya	US Centres for Disease Control and Prevention, USA
Malawi	University of North Carolina Project	Lilongwe	University of North Carolina at Chapel Hill, USA
Mozambique	Centro de Investigação em Saúde de Manhiça	Manhiça	Barcelona Centre for International Health Research (CRESIB), Hospital Clinic - Universitat de Barcelona
Tanzania	Ifakara Health Institute (IHI), Bagamoyo Branch	Bagamoyo	Swiss Tropical and Public Health Institute, Switzerland
Tanzania	National Institute for Medical Research, Korogwe Branch	Korogwe	London School of Hygiene and Tropical Medicine, UK Centre for Medical Parasitology at University of Copenhagen and Copenhagen University Hospital, Denmark Kilimanjaro Christian Medical College, Tanzania

Table S2. Algorithm for the evaluation of a hospital admission as a potential case of severe malaria.

For all acute hospital admissions (except planned admissions for medical investigation/care or elective surgery or trauma admissions), a blood sample was taken for evaluation of:
Malaria parasite density
Blood culture
Haemoglobin
Blood glucose, lactate and base excess
Lumbar puncture was indicated by the presence of:
Seizure except simple febrile seizure (defined as a seizure associated with fever, which lasts for 5 minutes or less, generalized as opposed to focal, not followed by transient or persistent neurological abnormalities, occurring in a child ≥ 6 months of age, with full recovery within 1 hour)
Blantyre Coma Score < 5 (children ≤ 9 months of age < 4 [in association with best motor response of 1])[1]
Prostration in a child < 3 year of age
Meningism/stiff neck/bulging fontanelle
Clinician's judgment
Chest X-ray (CXR) was indicated by the presence of:
Tachypnea (≥ 50 breaths per minute in a child < 1 year and ≥ 40 breaths per minute in a child ≥ 1 year)[2]
Lower chest wall indrawing
Abnormally deep breathing
Clinician's judgment

1. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989;**71**:441-59.
2. Berkley JA, Ross A, Mwangi I et al. Prognostic indicators of early and late death in children admitted to district hospital in Kenya: cohort study. *BMJ* 2003;**326**:361-6.

Table S3. Case definitions of severe malaria.

Primary case definition	*P. falciparum* > 5000 parasites per mm^3	**AND** one or more marker of disease severity: • Prostration • Respiratory distress • Blantyre score ≤ 2 • Seizures 2 or more • Hypoglycaemia < 2·2 mmol/L • Acidosis: base excess ≤ -10·0 mmol/L • Lactate ≥ 5·0 mmol/L • Anaemia < 50 g/L **AND** without diagnosis of a co-morbidity: • Radiographically proven pneumonia • Meningitis on CSF examination • Positive blood culture • Gastroenteritis with dehydration
Secondary case definition	*P. falciparum* > 5000 parasites per mm^3	**AND** one or more marker of disease severity without excluding co-morbidity

Prostration = in an acutely sick child, the inability to perform previously-acquired motor function: in a child previously able to stand, inability to stand; in a child previously able to sit, inability to sit and in a very young child, inability to suck.
Respiratory distress = lower chest wall indrawing or abnormally deep breathing.
Two or more seizures = two or more seizures occurring in the total time period including 24 hours prior to admission time in the emergency room and during hospitalization.
Radiographically proven pneumonia = a consolidation or pleural effusion defined per protocol on a chest x-ray taken within 72 hours of admission.
Meningitis on cerebrospinal fluid (CSF) examination = white blood cells ≥ 50 $x10^6$/L or positive culture of compatible organism or latex agglutination test positive for Hib, pneumococcal or meningococcal antigen.
Gastroenteritis with dehydration = history of three or more loose or watery stools in previous 24 hours, an observed watery stool and decreased skin turgor (> 2 seconds for skin to return following skin pinch).
Positive blood culture = defined per protocol on a blood culture taken within 72 hours of admission.

Table S4. Incidence of clinical malaria (secondary case definition) among infants in the 6-12 weeks age category control group during a 12-month follow-up period post dose 3 ordered by increasing malaria incidence.

All episodes of clinical malaria secondary case definition (per-protocol population for efficacy)	Control group (C3C)			
	N	**n**	**T (year)**	**n/T**
Kilifi	102	3	95·9	0·03
Korogwe	183	16	170·8	0·09
Manhiça	188	22	175·4	0·13
Lambaréné	62	11	57·1	0·19
Bagamoyo	244	47	227·9	0·21
Lilongwe	258	149	210·6	0·71
Agogo	221	298	209·9	1·42
Kombewa	196	372	166·5	2·23
Kintampo	99	194	84·7	2·29
Nanoro	225	605	182·2	3·32
Siaya	229	749	175·3	4·27
Overall	**2007**	**2466**	**1756·2**	**1·40**
All episodes of clinical malaria secondary case definition (intention-to-treat population)	**N**	**n**	**T (year)**	**n/T**
Kilifi	105	3	116·7	0·03
Korogwe	195	16	220·6	0·07
Manhiça	212	27	237·2	0·11
Lambaréné	68	14	71·2	0·2
Bagamoyo	269	53	296·9	0·18
Lilongwe	279	164	283·2	0·58
Agogo	230	325	263·7	1·23
Kombewa	210	424	213·1	1·99
Kintampo	110	227	114·6	1·98
Nanoro	228	693	231·4	2·99
Siaya	273	945	253·6	3·73
Overall	**2179**	**2891**	**2302·2**	**1·26**

The incidence of clinical malaria meeting the secondary case definition in infants in the control group during 12 months of follow-up was used to categorize malaria incidence across study sites. For all tables and figures reported here, study sites are presented from the lowest to the highest incidence of clinical malaria.

Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥ 37·5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre.

N = number of subjects included in each group.

n = number of episodes included in each group.

T(year) = person years at risk.

n/T = person year rate in each group.

Table S5. Percentage of subjects reporting serious adverse events until the end of the extension phase among children in the 5-17 months age category (intention-to-treat population).

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one SAE		720	24·2	22·7	25·8	752	25·3	23·7	26·9	846	28·4	26·8	30·1
At least one SAE excluding malaria		673	22·6	21·1	24·2	704	23·7	22·2	25·3	784	26·4	24·8	28·0
Fatalities		61	2·0	1·6	2·6	51	1·7	1·3	2·3	46	1·5	1·1	2·1
At least one related SAE		8	0·3	0·1	0·5	4	0·1	0·0	0·3	1	0·0	0·0	0·2
All SAEs													
Primary System Organ Class	**Preferred Term**												
Blood and lymphatic system disorders	Anaemia	126	4·2	3·5	5·0	150	5·0	4·3	5·9	197	6·6	5·8	7·6
	Disseminated intravascular coagulation	1	0·0	0·0	02	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Hypochromic anaemia	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Intravascular haemolysis	0	0·0	0·0	0·1	1	0·0	0·0	02	2	0·1	0·0	0·2
	Leukaemoid reaction	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Lymphadenitis	4	0·1	0·0	0·3	3	0·1	0·0	0·3	1	0·0	0·0	0·2
	Neutropenia	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Pancytopenia	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
Cardiac disorders	Cardiac failure	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Cardiomyopathy	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
Congenital, familial and genetic disorders	Atrial septal defect	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Cerebral palsy	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Choledochal cyst	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Congenital megacolon	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Cryptorchism	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Glucose-6-phosphate dehydrogenase deficiency	0	0·0	0·0	0·1	2	0·1	0·0	0·2	0	0·0	0·0	0·1
	Hydrocele	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Phimosis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Sickle cell anaemia	1	0·0	0·0	0·2	4	0·1	0·0	0·3	1	0·0	0·0	0·2
	Sickle cell anaemia with crisis	4	0·1	0·0	0·3	4	01	0·0	0·3	6	0·2	0·1	0·4
	Ventricular septal defect	0	0·0	0·0	0·1	0	0·0	0·0	0·1	2	0·1	0·0	0·2
Ear and labyrinth disorders	Deafness	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Hearing impaired	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
Gastrointestinal disorders	Aphthous stomatitis	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Colitis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Constipation	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Enteritis	10	0·3	0·2	0·6	18	0·6	0·4	1·0	15	0·5	0·3	0·8
	Food poisoning	1	0·0	0·0	0·2	0	0·0	0·0	0·1	2	0·1	0·0	0·2
	Gastritis	0	0·0	0·0	0·1	2	0·1	0·0	0·2	2	0·1	0·0	0·2
	Gastrointestinal haemorrhage	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Gastrointestinal motility disorder	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Gastro-oesophageal reflux disease	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Ileus paralytic	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Intestinal obstruction	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Intestinal perforation	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Intussusception	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Mouth ulceration	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Rectal prolapse	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Stomatitis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Stress ulcer	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Umbilical hernia	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Umbilical hernia, obstructive	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Upper gastrointestinal haemorrhage	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
General disorders and administration site conditions	Death	3	0·1	0·0	0·3	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Drowning	3	0·1	0·0	0·3	2	0·1	0·0	0·2	3	0·1	0·0	0·3
	Generalised oedema	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Hernia	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Hypothermia	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Injection site reaction	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Pyrexia	18	0·6	0·4	1·0	10	0·3	0·2	0·6	16	0·5	0·3	0·9
Hepatobiliary disorders	Cholecystitis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Hepatitis	0	0·0	0·0	0·1	2	0·1	0·0	0·2	1	0·0	0·0	0·2
	Hepatitis acute	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Hepatitis toxic	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
Immune system disorders	Anaphylactic reaction	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Hypersensitivity	0	0·0	0·0	0·1	3	0·1	0·0	0·3	0	0·0	0·0	0·1

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Infections and infestations	Abscess	7	0·2	0·1	0·5	7	0·2	0·1	0·5	5	0·2	0·1	0·4
	Abscess jaw	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Abscess limb	1	0·0	0·0	0·2	0	0·0	0·0	0·1	3	0·1	0·0	0·3
	Acarodermatitis	0	0·0	0·0	0·1	2	0·1	0·0	0·2	0	0·0	0·0	0·1
	Aids dementia complex	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Amoebiasis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Arthritis bacterial	2	0·1	0·0	0·2	7	0·2	0·1	0·5	1	0·0	0·0	0·2
	Ascariasis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Bacteraemia	0	0·0	0·0	0·1	2	0·1	0·0	0·2	1	0·0	0·0	0·2
	Bacterial infection	0	0·0	0·0	0·1	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Bone tuberculosis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Breast abscess	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Bronchiolitis	25	0·8	0·5	1·2	13	0·4	0·2	0·7	18	0·6	0·4	1·0
	Bronchitis	13	0·4	0·2	0·7	15	0·5	0·3	0·8	21	0·7	0·4	1·1
	Bronchopneumonia	33	1·1	0·8	1·6	35	1·2	0·8	1·6	40	1·3	1·0	1·8
	Bullous impetigo	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Burkholderia cepacia complex sepsis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Burn infection	1	0·0	0·0	0·2	2	0·1	0·0	0·2	0	0·0	0·0	0·1
	Cellulitis	8	0·3	0·1	0·5	7	0·2	0·1	0·5	6	0·2	0·1	0·4
	Cellulitis of male external genital organ	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Cellulitis orbital	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Cellulitis pharyngeal	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Cerebral malaria	4	0·1	0·0	0·3	4	0·1	0·0	0·3	0	0·0	0·0	0·1
	Cholera	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Conjunctivitis	2	0·1	0·0	0·2	4	0·1	0·0	0·3	0	0·0	0·0	0·1
	Conjunctivitis bacterial	0	0·0	0·0	0·1	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Croup infectious	0	0·0	0·0	0·1	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Dermatitis infected	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Disseminated tuberculosis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Dysentery	11	0·4	0·2	0·7	13	0·4	0·2	0·7	9	0·3	0·1	0·6
	Eczema infected	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Empyema	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Encephalitis	4	0·1	0·0	0·3	1	0·0	0·0	0·2	2	0·1	0·0	0·2
	Encephalitis viral	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Encephalomyelitis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Enterococcal sepsis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Erysipelas	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Escherichia urinary tract infection	1	0·0	0·0	0·2	0	0·0	0·0	0·1	2	0·1	0·0	0·2
	Furuncle	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Gastroenteritis	153	5·1	4·4	6·0	148	5·0	4·2	5·8	177	6·0	5·1	6·9
	Gastroenteritis *Escherichia coli*	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Gastroenteritis salmonella	2	0·1	0·0	0·2	3	0·1	0·0	0·3	0	0·0	0·0	0·1
	Gastroenteritis shigella	0	0·0	0·0	0·1	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Gastroenteritis viral	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Gastrointestinal candidiasis	0	0·0	0·0	0·1	2	0·1	0·0	0·2	0	0·0	0·0	0·1
	Giardiasis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Gingivitis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Groin abscess	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Haemophilus sepsis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Helminthic infection	2	0·1	0·0	0·2	8	0·3	0·1	0·5	6	0·2	0·1	0·4
	Hepatitis A	2	0·1	0·0	0·2	2	0·1	0·0	0·2	1	0·0	0·0	0·2
	HIV infection	22	0·7	0·5	1·1	19	0·6	0·4	1·0	18	0·6	0·4	1·0
	HIV infection WHO clinical stage II	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	HIV infection WHO clinical stage IV	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Impetigo	1	0·0	0·0	0·2	2	0·1	0·0	0·2	3	0·1	0·0	0·3
	Infected skin ulcer	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Injection site cellulitis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Klebsiella sepsis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Laryngitis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Lobar pneumonia	6	0·2	0·1	0·4	5	0·2	0·1	0·4	7	0·2	0·1	0·5
	Lower respiratory tract infection	2	0·1	0·0	0·2	3	0·1	0·0	0·3	6	0·2	0·1	0·4
	Ludwig angina	2	0·1	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Lymph node abscess	0	0·0	0·0	0·1	2	0·1	0·0	0·2	0	0·0	0·0	0·1
	Lymph node tuberculosis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Lymphadenitis bacterial	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Malaria	294	9·9	8·8	11·0	342	11·5	10·4	12·7	421	14·2	12·9	15·5
	Mastoiditis	2	0·1	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Measles	7	0·2	0·1	0·5	2	0·1	0·0	0·2	5	0·2	0·1	0·4
	Meningitis	5	0·2	0·1	0·4	5	0·2	0·1	0·4	1	0·0	0·0	0·2
	Meningitis haemophilus	1	0·0	0·0	0·2	2	0·1	0·0	0·2	0	0·0	0·0	0·1
	Meningitis meningococcal	3	0·1	0·0	0·3	2	0·1	0·0	0·2	0	0·0	0·0	0·1
	Meningitis pneumococcal	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Meningitis tuberculous	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Meningitis viral	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Mycobacterium ulcerans infection	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Nasopharyngitis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Oral candidiasis	5	0·2	0·1	0·4	5	0·2	0·1	0·4	4	0·1	0·0	0·3
	Oropharyngeal candidiasis	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Osteomyelitis	3	0·1	0·0	0·3	2	0·1	0·0	0·2	3	0·1	0·0	0·3
	Otitis externa	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Otitis media	19	0·6	0·4	1·0	10	0·3	0·2	0·6	22	0·7	0·5	1·1
	Otitis media acute	2	0·1	0·0	0·2	2	0·1	0·0	0·2	2	0·1	0·0	0·2
	Otitis media chronic	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Parotitis	0	0·0	0·0	0·1	2	0·1	0·0	0·2	1	0·0	0·0	0·2
	Perineal abscess	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Periorbital cellulitis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Pharyngitis	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Plasmodium ovale infection	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Pneumococcal sepsis	5	0·2	0·1	0·4	4	0·1	0·0	0·3	3	0·1	0·0	0·3
	Pneumocystis jirovecii pneumonia	2	0·1	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Pneumonia	202	6·8	5·9	7·8	215	7·2	6·3	8·2	223	7·5	6·6	8·5
	Pneumonia streptococcal	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Postoperative wound infection	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Pseudomonal sepsis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Pulmonary tuberculosis	7	0·2	0·1	0·5	1	0·0	0·0	0·2	4	0·1	0·0	0·3
	Pyelonephritis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pyoderma	1	0·0	0·0	0·2	1	0·0	0·0	0·2	3	0·1	0·0	0·3
	Pyomyositis	1	0·0	0·0	0·2	1	0·0	0·0	0·2	3	0·1	0·0	0·3
	Rabies	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Respiratory tract infection	2	0·1	0·0	0·2	2	0·1	00	0·2	2	0·1	0·0	0·2
	Salmonella sepsis	36	1·2	0·8	1·7	34	1·1	0·8	1·6	42	1·4	1·0	1·9
	Salmonellosis	1	0·0	0·0	0·2	3	0·1	0·0	0·3	2	0·1	0·0	0·2
	Schistosomiasis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Sepsis	33	1·1	0·8	1·6	27	0·9	0·6	1·3	43	1·4	1·0	1·9
	Shigella infection	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Skin bacterial infection	2	0·1	0·0	0·2	0	0·0	0·0	01	2	0·1	0·0	0·2
	Skin infection	3	0·1	0·0	0·3	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Staphylococcal sepsis	3	0·1	0·0	0·3	6	0·2	0·1	0·4	1	0·0	0·0	0·2
	Staphylococcal skin infection	1	0·0	0·0	0·2	2	0·1	0·0	0·2	2	0·1	0·0	0·2
	Streptococcal infection	0	0·0	0·0	0·1	1	0·0	0·0	02	0	0·0	0·0	0·1
	Streptococcal sepsis	1	0·0	0·0	0·2	1	0·0	0·0	0·2	2	0·1	0·0	0·2
	Subcutaneous abscess	5	0·2	0·1	0·4	4	0·1	0·0	0·3	2	0·1	0·0	0·2
	Taeniasis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Tinea capitis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Tonsillitis	1	0·0	0·0	0·2	1	0·0	0·0	0·2	3	0·1	0·0	0·3
	Toxic shock syndrome	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Tracheobronchitis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Trichiniasis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Tuberculosis	4	0·1	0·0	0·3	5	0·2	0·1	0·4	6	0·2	0·1	0·4
	Typhoid fever	1	0·0	0·0	0·2	1	0·0	0·0	0·2	3	0·1	0·0	0·3
	Upper respiratory tract infection	29	1·0	0·7	1·4	39	1·3	0·9	1·8	43	1·4	1·0	1·9
	Urinary tract infection	22	0·7	0·5	1·1	23	0·8	0·5	1·2	28	0·9	0·6	1·4
	Urinary tract infection bacterial	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Urinary tract infection pseudomonal	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Varicella	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Wound infection	1	0·0	0·0	0·2	1	0·0	0·0	0·2	2	0·1	0·0	0·2
	Wound sepsis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Injury, poisoning and procedural complications	Accidental exposure to product	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Accidental poisoning	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Animal bite	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Arthropod sting	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Bronchitis chemical	3	0·1	0·0	0·3	1	0·0	0·0	0·2	2	0·1	0·0	0·2
	Burns first degree	2	0·1	0·0	0·2	2	0·1	0·0	0·2	1	0·0	0·0	0·2
	Burns second degree	1	0·0	0·0	0·2	5	0·2	0·1	0·4	2	0·1	0·0	0·2
	Chemical injury	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Chemical poisoning	1	0·0	0·0	0·2	1	0·0	0·0	0·2	7	0·2	0·1	0·5
	Crush injury	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Disinfectant poisoning	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Dislocation of vertebra	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Exposure to toxic agent	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Eye contusion	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Eye injury	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Femur fracture	3	0·1	0·0	0·3	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Foreign body	4	0·1	0·0	0·3	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Foreign body aspiration	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Fractured skull depressed	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Head injury	1	0·0	0·0	0·2	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Herbal toxicity	2	0·1	0·0	0·2	3	0·1	0·0	0·3	2	0·1	0·0	0·2
	Humerus fracture	1	0·0	0·0	0·2	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Joint injury	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Laceration	0	0·0	0·0	0·1	1	0·0	0·0	0·2	2	0·1	0·0	0·2
	Limb traumatic amputation	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Penis injury	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Petroleum distillate poisoning	2	0·1	0·0	0·2	2	0·1	0·0	0·2	4	0·1	0·0	0·3
	Pneumonitis chemical	4	0·1	0·0	0·3	1	0·0	0·0	0·2	4	0·1	0·0	0·3
	Poisoning	0	0·0	0·0	0·1	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Pulmonary contusion	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Road traffic accident	1	0·0	0·0	0·2	0	0·0	0·0	0·1	2	0·1	0·0	0·2
	Sciatic nerve injury	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Skin injury	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Snake bite	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Soft tissue injury	2	0·1	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Thermal burn	15	0·5	0·3	0·8	10	0·3	0·2	0·6	15	0·5	0·3	0·8
	Tibia fracture	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Wound	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
Metabolism and nutrition disorders	Dehydration	1	0·0	0·0	0·2	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Failure to thrive	1	0·0	0·0	0·2	0	0·0	0·0	0·1	2	0·1	0·0	0·2
	Hypoglycaemia	10	0·3	0·2	0·6	10	0·3	0·2	0·6	18	0·6	0·4	1·0
	Hypokalaemia	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Hypoproteinaemia	0	0·0	0·0	0·1	2	0·1	0·0	0·2	1	0·0	0·0	0·2
	Kwashiorkor	11	0·4	0·2	0·7	4	0·1	0·0	0·3	17	0·6	0·3	0·9
	Malnutrition	27	0·9	0·6	1·3	27	0·9	0·6	1·3	21	0·7	0·4	1·1
	Marasmus	6	0·2	0·1	0·4	8	0·3	0·1	0·5	4	0·1	0·0	0·3
	Underweight	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
Musculoskeletal and connective tissue disorders	Arthritis	2	0·1	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Joint effusion	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Myositis	2	0·1	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Torticollis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Brain neoplasm	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
Nervous system disorders	Arachnoid cyst	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Cerebral atrophy	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Convulsion	57	1·9	1·5	2·5	45	1·5	1·1	2·0	58	2·0	1·5	2·5
	Depressed level of consciousness	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Encephalopathy	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Epilepsy	3	0·1	0·0	0·3	10	0·3	0·2	0·6	2	0·1	0·0	0·2
	Febrile convulsion	159	5·3	4·6	6·2	184	6·2	5·4	7·1	164	5·5	4·7	6·4
	Haemorrhage intracranial	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Hemiparesis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Hemiplegia	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Hydrocephalus	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Meningism	0	0·0	0·0	0·1	0	0·0	0·0	0·1	2	0·1	0·0	0·2

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Mental retardation	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Paraparesis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Speech disorder developmental	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
Psychiatric disorders	Neurodevelopmental disorder	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
Renal and urinary disorders	Nephrotic syndrome	0	0·0	0·0	0·1	1	0·0	0·0	0·2	1	0·0	0·0	0·2
Reproductive system and breast disorders	Acquired phimosis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
Respiratory, thoracic and mediastinal disorders	Asphyxia	1	0·0	0·0	0·2	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Aspiration	1	0·0	0·0	0·2	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Asthma	9	0·3	0·1	0·6	6	0·2	0·1	0·4	8	0·3	0·1	0·5
	Bronchospasm	2	0·1	0·0	0·2	0	0·0	0·0	0·1	3	0·1	0·0	0·3
	Cough	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Epistaxis	0	0·0	0·0	0·1	0	0·0	0·0	0·1	2	0·1	0·0	0·2
	Interstitial lung disease	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Pleural effusion	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Pneumonia aspiration	7	0·2	0·1	0·5	1	0·0	0·0	0·2	6	0·2	0·1	0·4
	Pulmonary oedema	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Respiratory acidosis	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Respiratory disorder	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
Skin and subcutaneous tissue disorders	Dermatitis	1	0·0	0·0	0·2	1	0·0	0·0	0·2	2	0·1	0·0	0·2
	Dermatitis allergic	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Erythema multiforme	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Rash	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Rash maculo-papular	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Rash papular	0	0·0	0·0	0·1	1	0·0	0·0	0·2	0	0·0	0·0	0·1
	Skin lesion	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
	Stevens-Johnson syndrome	0	0·0	0·0	0·1	0	0·0	0·0	01	1	0·0	0·0	0·2
	Urticaria	1	0·0	0·0	0·2	1	0·0	0·0	0·2	1	0·0	0·0	0·2
	Vitiligo	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2
Social circumstances	Child abuse	1	0·0	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Sexual abuse	2	0·1	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
Vascular disorders	Haematoma	2	0·1	0·0	0·2	0	0·0	0·0	0·1	0	0·0	0·0	0·1
	Hypovolaemic shock	0	0·0	0·0	0·1	0	0·0	0·0	0·1	1	0·0	0·0	0·2

		R3R N = 2976				R3C N = 2972				C3C N = 2974			
				95% CI				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Shock	0	0·0	0·0	0·1	3	0·1	0·0	0·3	5	0·2	0·1	0·4

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
At least one SAE = at least one SAE experienced (regardless of the MedDRA Preferred Term).
At least one SAE excluding malaria = at least one SAE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.
SAE = serious adverse event.
N = number of subjects with at least one administered dose.
n/% = number/percentage of subjects reporting the SAE at least once.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S6. Percentage of subjects reporting serious adverse events until the end of the extension phase among infants in the 6-12 weeks age category (intention-to-treat population).

		R3R N = 2180				R3C N = 2178				C3C N = 2179			
				95% CI				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one SAE		580	26·6	24·8	28·5	602	27·6	25·8	29·6	619	28·4	26·5	30·4
At least one SAE excluding malaria		562	25·8	24·0	27·7	582	26·7	24·9	28·6	591	27·1	25·3	29·0
Fatalities		51	2·3	1·7	3·1	55	2·5	1·9	3·3	42	1·9	1·4	2·6
At least one related SAE		6	0·3	0·1	0·6	1	0·0	0·0	0·3	3	0·1	0·0	0·4
All SAEs													
Primary System Organ Class	**Preferred Term**												
Blood and lymphatic system disorders	Anaemia	90	4·1	3·3	5·1	106	4·9	4·0	5·9	116	5·3	4·4	6·4
	Haemolysis	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Haemolytic anaemia	1	0·0	0·0	0·3	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Lymphadenitis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	2	0·1	0·0	0·3
	Thrombocytopenia	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
Cardiac disorders	Cardiac arrest	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Pericardial effusion	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
Congenital, familial and genetic disorders	Cerebral palsy	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Congenital megacolon	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Fallot's tetralogy	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Glucose-6-phosphate dehydrogenase deficiency	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Phimosis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Sickle cell anaemia	1	0·0	0·0	0·3	3	0·1	0·0	0·4	5	0·2	0·1	0·5
	Sickle cell anaemia with crisis	1	0·0	0·0	0·3	4	0·2	0·1	0·5	5	0·2	0·1	0·5
	Trisomy 21	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Urethral valves	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
Ear and labyrinth disorders	Deafness	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
Eye disorders	Periorbital oedema	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
Gastrointestinal disorders	Constipation	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Enteritis	7	0·3	0·1	0·7	10	0·5	0·2	0·8	18	0·8	0·5	1·3
	Food poisoning	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Gastritis	2	0·1	0·0	0·3	1	0·0	0·0	0·3	4	0·2	0·1	0·5
	Haematemesis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Inguinal hernia	0	0·0	0·0	0·2	1	0·0	0·0	0·3	3	0·1	0·0	0·4

		R3R N = 2180				R3C N = 2178				C3C N = 2179			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Intestinal obstruction	2	0·1	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Intussusception	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Rectal polyp	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Rectal prolapse	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Stomatitis	2	0·1	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Vomiting	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
General disorders and administration site conditions	Death	2	0·1	0·0	0·3	1	0·0	0·0	0·3	3	0·1	0·0	0·4
	Drowning	1	0·0	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Generalised oedema	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Hypothermia	1	0·0	0·0	0·3	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Injection site reaction	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Pyrexia	15	0·7	0·4	1·1	11	0·5	0·3	0·9	18	0·8	0·5	1·3
Hepatobiliary disorders	Cholecystitis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Hepatitis	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Hepatitis acute	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
Immune system disorders	Allergy to arthropod sting	0	0·0	0·0	0·2	0	0·0	0·0	0·2	2	0·1	0·0	0·3
	Anaphylactic reaction	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Drug hypersensitivity	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Hypersensitivity	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Immune reconstitution inflammatory syndrome	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
Infections and infestations	Abscess	4	0·2	0·1	0·5	8	0·4	0·2	0·7	5	0·2	0·1	0·5
	Abscess limb	0	0·0	0·0	0·2	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Abscess neck	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Amoebiasis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Arthritis bacterial	3	0·1	0·0	0·4	3	0·1	0·0	0·4	1	0·0	0·0	0·3
	Atypical pneumonia	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Bacterial infection	0	0·0	0·0	0·2	0	0·0	0·0	0·2	2	0·1	0·0	0·3
	Brain abscess	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Bronchiolitis	19	0·9	0·5	1·4	13	0·6	0·3	1·0	24	1·1	0·7	1·6
	Bronchitis	6	0·3	0·1	0·6	11	0·5	0·3	0·9	3	0·1	0·0	0·4
	Bronchopneumonia	35	1·6	1·1	2·2	19	0·9	0·5	1·4	34	1·6	1·1	2·2
	Bullous impetigo	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2

		R3R N = 2180				R3C N = 2178				C3C N = 2179			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Burn infection	0	0·0	0·0	0·2	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Candida infection	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Cellulitis	6	0·3	0·1	0·6	4	0·2	0·1	0·5	6	0·3	0·1	0·6
	Central nervous system viral infection	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Cerebral malaria	1	0·0	0·0	0·3	1	0·0	0·0	0·3	2	0·1	0·0	0·3
	Conjunctivitis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Conjunctivitis bacterial	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Dysentery	4	0·2	0·1	0·5	6	0·3	0·1	0·6	7	0·3	0·1	0·7
	Encephalitis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Encephalitis viral	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Enterococcal sepsis	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Escherichia sepsis	1	0·0	0·0	0·3	1	0·0	0·0	0·3	2	0·1	0·0	0·3
	Escherichia urinary tract infection	1	0·0	0·0	0·3	2	0·1	0·0	0·3	2	0·1	0·0	0·3
	Exanthema subitum	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Febrile infection	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Gastroenteritis	162	7·4	6·4	8·6	171	7·9	6·8	9·1	171	7·8	6·8	9·1
	Gastroenteritis salmonella	5	0·2	0·1	0·5	2	0·1	0·0	0·3	4	0·2	0·1	0·5
	Gastroenteritis shigella	0	0·0	0·0	0·2	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Giardiasis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Groin abscess	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Haemophilus sepsis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Helminthic infection	1	0·0	0·0	0·3	2	0·1	0·0	0·3	1	0·0	0·0	0·3
	Hepatitis A	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Hepatitis B	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Hepatitis infectious	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	HIV associated nephropathy	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	HIV infection	20	0·9	0·6	1·4	16	0·7	0·4	1·2	12	0·6	0·3	1·0
	HIV infection WHO clinical stage III	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	HIV infection WHO clinical stage IV	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Impetigo	2	0·1	0·0	0·3	2	0·1	0·0	0·3	1	0·0	0·0	0·3
	Infection	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Injection site abscess	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3

		R3R N = 2180				R3C N = 2178				C3C N = 2179			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Laryngitis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Listeria sepsis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Liver abscess	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Lobar pneumonia	8	0·4	0·2	0·7	9	0·4	0·2	0·8	7	0·3	0·1	0·7
	Lower respiratory tract infection	0	0·0	0·0	0·2	4	0·2	0·1	0·5	2	0·1	0·0	0·3
	Ludwig angina	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Lymph node abscess	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Malaria	180	8·3	7·1	9·5	208	9·6	8·3	10·9	233	10·7	9·4	12·1
	Mastoiditis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Measles	14	0·6	0·4	1·1	10	0·5	0·2	0·8	8	0·4	0·2	0·7
	Meningitis	2	0·1	0·0	0·3	3	0·1	0·0	0·4	3	0·1	0·0	0·4
	Meningitis haemophilus	0	0·0	0·0	0·2	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Meningitis pneumococcal	1	0·0	0·0	0·3	2	0·1	0·0	0·3	2	0·1	0·0	0·3
	Meningitis salmonella	2	0·1	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Moraxella infection	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Mumps	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Oral candidiasis	1	0·0	0·0	0·3	2	0·1	0·0	0·3	1	0·0	0·0	0·3
	Oropharyngeal candidiasis	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Osteomyelitis	1	0·0	0·0	0·3	1	0·0	0·0	0·3	2	0·1	0·0	0·3
	Otitis externa	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Otitis media	11	0·5	0·3	0·9	11	0·5	0·3	0·9	7	0·3	0·1	0·7
	Otitis media acute	2	0·1	0·0	0·3	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Parotitis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Periorbital cellulitis	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Peritonitis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Pharyngitis	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Pneumococcal bacteraemia	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Pneumococcal sepsis	5	0·2	0·1	0·5	4	0·2	0·1	0·5	3	0·1	0·0	0·4
	Pneumocystis jirovecii pneumonia	4	0·2	0·1	0·5	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Pneumonia	217	10·0	8·7	11·3	206	9·5	8·3	10·8	202	9·3	8·1	10·6
	Pneumonia pneumococcal	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Pneumonia streptococcal	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2

		R3R N = 2180				R3C N = 2178				C3C N = 2179			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pneumonia viral	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Pulmonary tuberculosis	6	0·3	0·1	0·6	6	0·3	0·1	0·6	2	0·1	0·0	0·3
	Pyomyositis	1	0·0	0·0	0·3	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Respiratory tract infection	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Rubella	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Salmonella bacteraemia	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Salmonella sepsis	25	1·1	0·7	1·7	34	1·6	1·1	2·2	37	1·7	1·2	2·3
	Sepsis	23	1·1	0·7	1·6	15	0·7	0·4	1·1	13	0·6	0·3	1·0
	Septic shock	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Staphylococcal sepsis	5	0·2	0·1	0·5	5	0·2	0·1	0·5	2	0·1	0·0	0·3
	Staphylococcal skin infection	1	0·0	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Streptococcal sepsis	1	0·0	0·0	0·3	1	0·0	0·0	0·3	2	0·1	0·0	0·3
	Subcutaneous abscess	6	0·3	0·1	0·6	1	0·0	0·0	0·3	3	0·1	0·0	0·4
	Superinfection	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Tonsillitis	1	0·0	0·0	0·3	2	0·1	0·0	0·3	0	0·0	0·0	0·2
	Tuberculosis	2	0·1	0·0	0·3	4	0·2	0·1	0·5	3	0·1	0·0	0·4
	Typhoid fever	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Upper respiratory tract infection	19	0·9	0·5	1·4	31	1·4	1·0	2·0	24	1·1	0·7	1·6
	Urinary tract infection	11	0·5	0·3	0·9	15	0·7	0·4	1·1	22	1·0	0·6	1·5
	Urosepsis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Vaginal infection	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Varicella	2	0·1	0·0	0·3	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Viral infection	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
Injury, poisoning and procedural complications	Burns first degree	2	0·1	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Burns second degree	3	0·1	0·0	0·4	2	0·1	0·0	0·3	3	0·1	0·0	0·4
	Clavicle fracture	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Femur fracture	2	0·1	0·0	0·3	2	0·1	0·0	0·3	2	0·1	0·0	0·3
	Greenstick fracture	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Head injury	0	0·0	0·0	0·2	4	0·2	0·1	0·5	0	0·0	0·0	0·2
	Herbal toxicity	0	0·0	0·0	0·2	2	0·1	0·0	0·3	3	0·1	0·0	0·4
	Human bite	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Humerus fracture	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2

		R3R N = 2180				R3C N = 2178				C3C N = 2179			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Limb injury	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Petroleum distillate poisoning	1	0·0	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Pneumonitis chemical	2	0·1	0·0	0·3	2	0·1	0·0	0·3	0	0·0	0·0	0·2
	Soft tissue injury	1	0·0	0·0	0·3	1	0·0	0·0	0·3	3	0·1	0·0	0·4
	Thermal burn	14	0·6	0·4	1·1	9	0·4	0·2	0·8	11	0·5	0·3	0·9
	Tibia fracture	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Vaccination failure	1	0·0	0·0	0·3	1	0·0	0·0	0·3	2	0·1	0·0	0·3
	Wrist fracture	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
Metabolism and nutrition disorders	Dehydration	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Failure to thrive	1	0·0	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Hyperkalaemia	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Hypoglycaemia	2	0·1	0·0	0·3	3	0·1	0·0	0·4	3	0·1	0·0	0·4
	Hypokalaemia	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Kwashiorkor	8	0·4	0·2	0·7	8	0·4	0·2	0·7	4	0·2	0·1	0·5
	Malnutrition	20	0·9	0·6	1·4	30	1·4	0·9	2·0	19	0·9	0·5	1·4
	Marasmus	6	0·3	0·1	0·6	5	0·2	0·1	0·5	7	0·3	0·1	0·7
	Metabolic acidosis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
Musculoskeletal and connective tissue disorders	Arthritis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Compartment syndrome	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Dactylitis	2	0·1	0·0	0·3	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Myositis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Osteoarthritis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Rickets	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Torticollis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Acute promyelocytic leukaemia	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Inflammatory pseudotumour	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Langerhans' cell histiocytosis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
Nervous system disorders	Cerebellar ataxia	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Convulsion	45	2·1	1·5	2·8	32	1·5	1·0	2·1	32	1·5	1·0	2·1
	Encephalomalacia	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Encephalopathy	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Epilepsy	1	0·0	0·0	0·3	2	0·1	0·0	0·3	0	0·0	0·0	0·2

		R3R N = 2180				R3C N = 2178				C3C N = 2179			
				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Febrile convulsion	100	4·6	3·7	5·6	90	4·1	3·3	5·1	101	4·6	3·8	5·6
	Hydrocephalus	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Loss of consciousness	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Metabolic encephalopathy	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Monoparesis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Myoclonus	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Paraparesis	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Uraemic encephalopathy	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
Psychiatric disorders	Neurodevelopmental disorder	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
Renal and urinary disorders	Glomerulonephritis	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Glomerulonephritis acute	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Hydronephrosis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Nephritis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Renal failure acute	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Renal tubular necrosis	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Urinary retention	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
Reproductive system and breast disorders	Acquired phimosis	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
Respiratory, thoracic and mediastinal disorders	Apnoeic attack	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Asthma	6	0·3	0·1	0·6	3	0·1	0·0	0·4	7	0·3	0·1	0·7
	Bronchial hyperreactivity	0	0·0	0·0	0·2	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Bronchospasm	3	0·1	0·0	0·4	5	0·2	0·1	0·5	5	0·2	0·1	0·5
	Obstructive airways disorder	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Pleural effusion	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Pneumonia aspiration	2	0·1	0·0	0·3	2	0·1	0·0	0·3	4	0·2	0·1	0·5
	Pneumonitis	0	0·0	0·0	0·2	1	0·0	0·0	0·3	1	0·0	0·0	0·3
	Respiratory arrest	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
Skin and subcutaneous tissue disorders	Dermatitis exfoliative	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
	Drug eruption	0	0·0	0·0	0·2	0	0·0	0·0	0·2	1	0·0	0·0	0·3
	Urticaria	1	0·0	0·0	0·3	0	0·0	0·0	0·2	0	0·0	0·0	0·2
Vascular disorders	Hypovolaemic shock	0	0·0	0·0	0·2	1	0·0	0·0	0·3	0	0·0	0·0	0·2
	Shock	1	0·0	0·0	0·3	2	0·1	0·0	0·3	4	0·2	0·1	0·5

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
At least one SAE = at least one SAE experienced (regardless of the MedDRA Preferred Term).
At least one SAE excluding malaria = at least one SAE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.
SAE = serious adverse event.
N = number of subjects with at least one administered dose.
n/% = number/percentage of subjects reporting the SAE at least once.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S7. Overall vaccine efficacy against clinical and severe malaria among children in the 5-17 months age category (per-protocol population for efficacy).

Efficacy against clinical malaria (primary case definition) of a primary schedule without booster (R3C)												
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Per-protocol population for efficacy		N	n	T (year)	n/T	N	n	T (year)	n/T	(%)	95% CI		p-value
Clinical malaria	M2·5-SE	2306	6597	7355·8	0·9	2336	8352	7352·4	1·14	26·2	20·8	31·2	<0·0001
	M2·5-M32	2306	4104	5093·3	0.8	2336	5813	5053·1	1·15	33·9	28·9	38·.6	<0·0001
	M2·5-M20*	4557	4257	6186·0	0·69	2328	3639	3100·4	1·17	45·7	41·7	49·5	<0·0001
	M21-M32	2057	1872	1956·1	0·96	2050	2135	1945·5	1·1	13·5	5·4	20·9	0·0015
	M33-SE	1838	2493	2266·4	1·1	1864	2539	2303·2	1·1	01	-9·9	9·1	0·9843
	M21-SE	2057	4365	4218·6	1·03	2050	4674	4244·9	1·1	8·2	0·4	15·3	0·0389
Efficacy against severe malaria (primary case definition) of a primary schedule without booster (R3C)												
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Per-protocol population for efficacy		N	n	Proportion affected		N	n	Proportion affected		(%)	95% CI		p-value
Severe malaria	M2·5-SE	2306	141	0·06		2336	135	0·06		-5·8	-35·0	17·0	0·6640
	M2·5-M32	2306	116	0·05		2336	120	0·05		2·1	-27·5	24·8	0·8938
	M2·5-M20*	4557	120	0·03		2328	95	0·04		35·5	14·6	51·1	0·0016
	M21-M32	2057	48	0·02		2051	32	0·02		-49·6	-142	6·3	00898
	M33-SE	1838	29	0·02		1864	16	0·01		-83·8	-262	3·4	00512
	M21-SE	2057	73	0·04		2051	48	0·02		-51·6	-123	-3·9	00264
Efficacy against clinical malaria (primary case definition) of a primary schedule with booster (R3R)												
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Per-protocol population for efficacy		N	n	T (year)	n/T	N	n	T (year)	n/T	(%)	95% CI		p-value
Clinical malaria	M2·5-SE	2276	5691	7247·4	0·79	2336	8352	7352·4	1·14	39·0	34·3	43·3	<0·0001
	M2·5-M32	2276	3438	5019·2	0·68	2336	5813	5053·1	1·15	46·1	41·8	50·1	<0·0001
	M2·5-M20*	4557	4257	6186·0	0·69	2328	3639	3100·4	1·17	45·7	41·7	49·5	<0·0001
	M21-M32	2017	1384	1933·4	0·72	2050	2135	1945·5	1·1	38·5	32·2	44·1	<0·0001
	M33-SE	1784	2254	2231·3	1·01	1864	2539	2303·2	1·1	14·6	5·8	22·6	0·0017
	M21-SE	2017	3637	4161·6	0·87	2050	4674	4244·9	1·1	27·6	21·2	33·5	<0·0001
Efficacy against severe malaria (primary case definition) of a primary schedule with booster (R3R)												
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Per-protocol population for efficacy		N	n	Proportion affected		N	n	Proportion affected		(%)	95% CI		p-value
Severe malaria	M2·5-SE	2276	94	0·04		2336	135	0·06		28·5	6·3	45·7	0·0100
	M2·5-M32	2276	79	0·03		2336	120	0·05		32·4	9·5	49·8	0·0058
	M25-M20*	4557	120	0·03		2328	95	0·04		35·5	14·6	51·1	0·0016

	M21-M32	2017	34	0·02	2051	32	0·02	-8·0	-80·8	35·3	0·8045
	M33-SE	1784	20	0·01	1864	16	0·01	-30·6	-170	35·7	05036
	M21-SE	2017	52	0·03	2051	48	0·02	-10·2	-66·6	27·0	0·6857
Incremental efficacy against clinical malaria (primary case definition) of a booster dose											
		R3R				**R3C**				**Point estimate of VE unadjusted for covariates**			
Per-protocol population for efficacy		**N**	**n**	**T (year)**	**n/T**	**N**	**n**	**T (year)**	**n/T**	**(%)**	**95% CI**		**p-value**
Clinical malaria	M21-SE	2017	3637	4161·6	0·87	2057	4365	4218·6	1·03	21·3	14·2	27·8	<0·0001
	M21-M32	2017	1384	1933·4	0·72	2057	1872	1956·1	0·96	29·0	21·6	35·6	<0·0001

*Data from previous analysis (comparing R3R+R3C versus C3C).
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects.
n (clinical malaria) = number of episodes meeting the case definition.
n (severe malaria) = number of subjects reporting at least one event in each group.
T = person years at risk.
n/T = incidence rate.
Proportion affected = proportion of subjects reporting at least one event.
VE = vaccine efficacy (negative binomial model for clinical malaria; 1-relative risk for severe malaria).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.
M2·5-SE = follow-up from 14 days post dose 3 (Month 2·5) to study end (end of extension phase).
M2·5-M32 = follow-up from 14 days post dose 3 (Month 2·5) to 30 months post dose 3 (Month 32).
M2·5-M20 = follow-up from 14 days post dose 3 (Month 2·5) to 18 months post dose 3 (Month 20).
M21-M32 = follow-up from day of booster dose to 30 months post dose 3 (Month 32).
M33-SE = follow-up from start of extension phase to study end (end of extension phase).
M21-SE = follow-up from day of booster dose to study end (end of extension phase).
SE = study end (the median follow-up in the 5-17 months age category was 48 months post dose 1).
Clinical malaria primary case definition = illness in a child brought to a study facility with a measured temperature of ≥ 37·5°C and *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria.
Severe malaria primary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.
For clinical malaria: p-value from negative binomial regression.
For severe malaria: p-value from two-sided Fisher exact test.

Table S8. Overall vaccine efficacy against clinical and severe malaria secondary case definition among children in the 5-17 months age category (intention-to-treat population).

Efficacy against clinical malaria (secondary case definition) of a primary schedule without booster (R3C)													
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**T (year)**	**n/T**	**N**	**n**	**T (year)**	**n/T**	**(%)**	**95% CI**		**p-value**
Clinical malaria	M0-SE	2972	11627	9876·3	1·18	2974	15029	9786·5	1·54	30·0	25·5	34·3	<0·0001
	M0-M32	2972	7325	7079·7	1·03	2974	10341	6950·9	1·49	35·7	31·3	39·7	<0·0001
Efficacy against severe malaria (secondary case definition) of a primary schedule without booster (R3C)													
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**Proportion affected**		**N**	**n**	**Proportion affected**		**(%)**	**95% CI**		**p-value**
Severe malaria	M0-SE	2972	186	0·06		2974	204	0·07		88	-11·8	25·6	0·3732
	M0-M32	2972	162	0·05		2974	183	0·06		11·4	-10·0	28·7	0·2672
Efficacy against clinical malaria (secondary case definition) of a primary schedule with booster (R3R)													
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**T (year)**	**n/T**	**N**	**n**	**T (year)**	**n/T**	**(%)**	**95% CI**		**p-value**
Clinical malaria	M0-SE	2976	10629	9803·4	1.08	2974	15029	9786·5	1·5	35·5	31·2	39·5	<0·0001
	M0-M32	2976	6615	7001·6	0.94	2974	10341	6950·9	1·5	41·6	37·6	45·4	<0·0001
Efficacy against severe malaria (secondary case definition) of a primary schedule with booster (R3R)													
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**Proportion affected**		**N**	**n**	**Proportion affected**		**(%)**	**95% CI**		**p-value**
Severe malaria	M0-SE	2976	141	0·05		2974	204	0·07		30·9	14·0	44·7	0·0005
	M0-M32	2976	121	0·04		2974	183	0·06		33·9	16·4	47·9	0·0003

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects.
n (clinical malaria) = number of episodes meeting the case definition.
n (severe malaria) = number of subjects reporting at least one event in each group.
T = person years at risk.
n/T = incidence rate.
Proportion affected = proportion of subjects reporting at least one event.
VE = vaccine efficacy (negative binomial model for clinical malaria; 1-relative risk for severe malaria).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.
M0-SE = follow-up from day of dose 1 (Month 0) to study end (end of extension phase).
M0-M32 = follow-up from day of dose 1 (Month 0) to 32 months post dose 1 (Month 32).
SE = study end (the median follow-up in the 5-17 months age category was 48 months post dose 1).

Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥37.5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre. This definition was used for this analysis as, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.
Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.
For clinical malaria: p-value from negative binomial regression.
For severe malaria: p-value from two-sided Fisher exact test.

Table S9. Vaccine efficacy against clinical malaria by age (5-11 months and 12-17 months) among children in the 5-17 months age category (intention-to-treat population).

Efficacy against clinical malaria (primary case definition) of a primary schedule without booster (R3C)													
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**T (year)**	**n/T**	**N**	**n**	**T (year)**	**n/T**	**(%)**	**95% CI**		**p-value**
Clinical malaria (M0-M32)	5-11 months	1676	2551	4052·7	0·63	1700	3557	4056·5	0·88	35·8	25·9	44·3	<0·0001
	12-17 months	1296	2160	3127·2	0·69	1274	3211	3032·0	1·06	39·2	29·6	47·5	<0·0001
	Overall	2972	4711	7180.0	0·66	2974	6768	7088·5	0·95	35·2	30·5	39·5	<0·0001
Efficacy against clinical malaria (primary case definition) of a primary schedule with booster (R3R)													
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**T (year)**	**n/T**	**N**	**n**	**T (year)**	**n/T**	**(%)**	**95% CI**		**p-value**
Clinical malaria (M0-M32)	5-11 months	1678	2181	3976·7	0·55	1700	3557	4056·5	0·88	42·8	34·2	50·3	<0·0001
	12-17 months	1298	1897	3123·1	0·61	1274	3211	3032·0	1·06	46·5	38.0	53·9	<0·0001
	Overall	2976	4078	7099·7	0·57	2974	6768	7088·5	0·95	43·9	39·7	47·8	<0·0001

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects.
n = number of episodes meeting the case definition.
T = person years at risk.
n/T = incidence rate.
VE = vaccine efficacy (negative binomial model for clinical malaria).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.
M0-M32 = follow-up from day of dose 1 (Month 0) to 32 months post dose 1 (Month 32).
Clinical malaria primary case definition = illness in a child brought to a study facility with a measured temperature of ≥ 37.5°C and *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria.
For clinical malaria: p-value from negative binomial regression.

Table S10. Outcome of all cases of severe malaria (secondary case definition) recorded among children in the 5-17 months age category (intention-to-treat population).

Time period	Outcome	R3R+R3C		R3R		R3C		C3C	
		N	n	N	n	N	n	N	n
M0-M20	Died	205	6	-	-	-	-	158	2
M0-M20	Survived with sequelae	205	0	-	-	-	-	158	0
M0-M20	Survived without sequelae	205	199	-	-	-	-	158	156
M21-SE	Died	-	-	76	3	103	6	76	2
M21-SE	Survived with sequelae	-	-	76	1	103	0	76	0
M21-SE	Survived without sequelae	-	-	76	72	103	97	76	74

R3R+R3C = RTS,S/AS01 primary schedule (combined R3R + R3C groups analysed over the period before the administration of the booster dose at Month 20).
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of cases of severe malaria secondary case definition.
n = number of cases of severe malaria secondary case definition of each outcome.
M0-M20 = follow-up from day of dose 1 (Month 0) to 20 months post dose 1 (Month 20).
M21-SE = follow-up from day of booster dose to study end (end of extension phase).
Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

Table S11. Outcome of all cases severe malaria (secondary case definition) recorded among infants in the 6-12 weeks age category (intention-to-treat population).

Time period	Outcome	R3R+R3C		R3R		R3C		C3C	
		N	n	N	n	N	n	N	n
M0-M20	Died	148	1	-	-	-	-	86	2
M0-M20	Survived with sequelae	148	0	-	-	-	-	86	0
M0-M20	Survived without sequelae	148	147	-	-	-	-	86	84
M21-SE	Died	-	-	53	3	63	2	68	0
M21-SE	Survived with sequelae	-	-	53	0	63	0	68	1
M21-SE	Survived without sequelae	-	-	53	50	63	61	68	67

R3R+R3C = RTS,S/AS01 primary schedule (combined R3R + R3C groups analysed over the period before the administration of the booster dose at Month 20).
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of cases of severe malaria secondary case definition.
n = number of cases of severe malaria secondary case definition of each outcome.
M0-M20 = follow-up from day of dose 1 (Month 0) to 20 months post dose 1 (Month 20).
M21-SE = follow-up from day of booster dose to study end (end of extension phase).
Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

Table S12. Overall vaccine efficacy against incident severe malaria anaemia, malaria hospitalization and fatal malaria until the end of the extension phase (M0-SE) among children in the 5-17 months age category (intention-to-treat population).

Efficacy of a primary schedule without booster (R3C)										
		R3C			**C3C**			**Point estimate of VE unadjusted for covariates**			
Intention-to-treat population		**N**	**n**	**Proportion affected**	**N**	**n**	**Proportion affected**	**(%)**	**95% CI**		**p-value**
Incident severe malaria anaemia	Case definition 1	2972	34	0·01	2974	44	0·01	22·7	-23.8	52·1	0·3050
	Case definition 2	2972	43	0·01	2974	54	0·02	20·3	-21·2	47·9	0·3060
Malaria hospitalization	Case definition 1	2972	286	0·1	2974	347	0·12	17·5	3·3	29·7	0·0116
	Case definition 2	2972	324	0·11	2974	400	0·13	18·9	5·9	30·2	0·0029
Fatal malaria	Primary case definition	2972	2	0	2974	1	0	-100·1	-12E3	89·6	0·6248
	Secondary case definition	2972	8	0	2974	4	0	-100·1	-808	46·4	0·2662
	ICD10 code	2972	17	0·01	2974	12	0	-41·8	-225	36·2	0·3603
Efficacy of a primary schedule with booster (R3R)										
		R3R			**C3C**			**Point estimate of VE unadjusted for covariates**			
Intention-to-treat population		**N**	**n**	**Proportion affected**	**N**	**n**	**Proportion affected**	**(%)**	**95% CI**		**p-value**
Incident severe malaria anaemia	Case definition 1	2976	23	0·01	2974	44	0·01	47·8	11·6	69·9	0·0099
	Case definition 2	2976	28	0·01	2974	54	0·02	48·2	16·7	68·4	0·0038
Malaria hospitalization	Case definition 1	2976	227	0·08	2974	347	0·12	34·6	22·5	44·9	<0·0001
	Case definition 2	2976	272	0·09	2974	400	0·13	32·0	20·5	42·0	<0·0001
Fatal malaria	Primary case definition	2976	1	0	2974	1	0	0·1	-7744	98·7	1·0000
	Secondary case definition	2976	7	0	2974	4	0	-74·9	-715	55·5	0·5484
	ICD10 code	2976	13	0	2974	12	0	-8·3	-160	54·5	1·0000

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects included in each group (without missing values).
n = number of subjects reporting at least one event in each group.
Proportion affected = proportion of subjects reporting at least one event.
VE (%) = vaccine efficacy (conditional method).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.
P-value = two-sided Fisher exact test.
M0-SE = follow-up from day of dose 1 (Month 0) to study end (end of extension phase). The median follow-up in the 5-17 months age category was 48 months post dose 1.

Incident severe malaria anaemia case definition 1 = a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 5000 parasites per cubic millimetre.
Incident severe malaria anaemia case definition 2 = a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 0 parasites per cubic millimetre.
Malaria hospitalization case definition 1 = a medical hospitalization with confirmed *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre.
Malaria hospitalization case definition 2 = a hospitalization which, in the judgment of the principal investigator, *P. falciparum* infection was the sole or a major contributing factor to the presentation.
Fatal malaria primary definition = a case of severe malaria meeting the primary case definition of severe malaria with a fatal outcome.
Fatal malaria secondary case definition = a case of severe malaria meeting the secondary case definition of severe malaria with a fatal outcome.
Fatal malaria (ICD10 code) = a fatal case associated with International Classification Disease (ICD10) code B50, B53, B54.

Table S13. Overall vaccine efficacy against serious illnesses until the end of the extension phase (M0-SE) among children in the 5-17 months age category (intention-to-treat population).

Efficacy of a primary schedule without booster (R3C)											
		R3C			C3C			Point estimate of VE unadjusted for covariates			
Intention-to-treat population		N	n	Proportion affected	N	n	Proportion affected	(%)	95% CI		p-value
Bacteraemia	Case definition 1	2972	60	0·02	2974	77	0·03	22·0	-10·7	45·3	0·1664
	Case definition 2 (Salmonella sepsis)	2972	35	0·01	2974	52	0·02	32·6	-5·4	57·4	0·0834
Pneumonia	Primary case definition	2972	100	0·03	2974	127	0·04	21·2	-3·2	40·0	0·0783
	Secondary case definition 1	2972	17	0·01	2974	22	0·01	22·7	-52·5	61·4	0·5210
All-cause hospitalization	Primary case definition	2972	682	0·23	2974	771	0·26	11·5	1·7	20·3	0·0079
All-cause mortality	Case definition 1	2972	51	0·02	2974	46	0·02	-10·9	-69·0	27·0	0·6107
	Case definition 2	2972	46	0·02	2974	41	0·01	-12·3	-75·4	27·9	0·5915
Blood transfusions	-	2972	91	0·03	2974	109	0·04	16·5	-11·4	37·5	0·2213
Efficacy of a primary schedule with booster (R3R)											
		R3R			C3C			Point estimate of VE unadjusted for covariates			
Intention-to-treat population		N	n	Proportion affected	N	n	Proportion affected	(%)	95% CI		p-value
Bacteraemia	Case definition 1	2976	70	0·02	2974	77	0·03	9·2	-27·2	35·2	0·5602
	Case definition 2 (Salmonella sepsis)	2976	41	0·01	2974	52	0·02	21·2	-21·0	49·0	0·2526
Pneumonia	Primary case definition	2976	125	0·04	2974	127	0·04	1·6	-26·9	23·8	0·8978
	Secondary case definition 1	2976	32	0·01	2974	22	0·01	-45·4	-163	18·1	0·2182
All-cause hospitalization	Primary case definition	2976	644	0·22	2974	771	0·26	16·5	7·2	24·9	0·0001
All-cause mortality	Case definition 1	2976	61	0·02	2974	46	0·02	-32·5	-98·7	11·1	0·1717
	Case definition 2	2976	54	0·02	2974	41	0·01	-31·6	-103	13·9	0·2144
Blood transfusions	-	2976	78	0·03	2974	109	0·04	28·5	3·5	47·2	0·0213

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects included in each group (without missing values).
n = number of subjects reporting at least one event in each group.
Proportion affected = proportion of subjects reporting at least one event.
VE(%) = vaccine efficacy (conditional method).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.
P-value = two-sided Fisher exact test.

M0-SE = follow-up from day of dose 1 (Month 0) to study end (end of extension phase). The median follow-up in the 5-17 months age category was 48 months post dose 1.
Bacteraemia case definition 1 = a child with a positive blood culture taken within 72 hours of admission.
Bacteraemia case definition 2 (Salmonella sepsis) = a child with a positive salmonella blood culture taken within 72 hours of admission.
Pneumonia primary case definition = cough or difficulty breathing (on history) and tachypnea (≥ 50 breaths per minute < 1 year, ≥ 40 breaths per minute ≥ 1year) and lower chest wall indrawing.
Pneumonia secondary case definition 1 = a case of pneumonia meeting the primary case definition of pneumonia with chest x-ray consolidation or pleural effusion on x-ray taken within 72 h of admission.
All-cause hospitalization primary case definition = a medical hospitalization of any cause, excluding planned admissions for medical investigation/care or elective surgery and trauma.
All-cause mortality case definition 1 = a fatality of any cause, including mortality in the community and in hospital.
All-cause mortality case definition 2 = a fatality of medical cause, including mortality in the community and in hospital and excluding trauma, which may be diagnosed by verbal autopsy.
Blood transfusion = a child with inpatient admission with documented blood transfusion.

Table S14. Vaccine efficacy against prevalent parasitaemia until the end of the extension phase among children in the 5-17 months age category (intention-to-treat population)

Efficacy of a primary schedule without booster (R3C)																
Intention-to-treat population	**Month 32**				**Month 44**				**SE early**				**SE late**			
Site	**VE (%)**	**LL**	**UL**	**p-value**	**VE (%)**	**LL**	**UL**	**p-value**	**VE (%)**	**LL**	**UL**	**p-value**	**VE (%)**	**LL**	**UL**	**p-value**
Kilifi	100	-132	100	0·1159												
Korogwe									100	-3833	100	1·0000				
Manhiça	-42·2	-397	56·7	0·5920	61·1	-62·2	93·3	0·2717					-23·2	-259	56·2	0·8082
Lambaréné	8·9	-83·0	55·2	0·8623	13·6	-161	72·6	0·7936	14·3	-214	78·5	1·0000	59·7	-68·0	93·1	0·2059
Bagamoyo	59·8	-76·1	93·3	0·2094												.
Lilongwe	-36·8	-447	62·6	0·7714	100	-5037	100	1·0000					100	-5157	100	1·0000
Agogo	53·6	9·7	77·3	0·0103	49·7	-17·9	80·1	0·1062					-22·2	-170	44·1	0·5724
Kombewa	8·8	-46·8	43·6	0·7099	-28·3	-92·5	14·3	0·1562	33·3	-68·4	74·2	0·3275	11·5	-41·1	44·9	0·6124
Kintampo	32·9	1·8	54·5	0·0169	29·0	-14·2	56·4	0·0972	22·0	-32·1	53·9	0·2811	5·9	-42·7	38·2	0·8096
Nanoro	44·6	8·8	67·0	0·0059	46·2	3·3	70·9	0·0126	39·6	-10·4	68·2	0·0143	37·7	5·1	59·6	0·0029
Siaya	15·3	-24·8	42·7	0·3198	7·7	-31·4	35·1	0·5706	16·4	-147	74·6	0·7442	5·7	-38·1	35·6	0·7305
Overall	**28·3**	**14·1**	**40·3**	**0·0001**	**15·5**	**-2·6**	**30·5**	**0·0573**	**28·1**	**1·3**	**47·8**	**0·0274**	**14·7**	**-3·0**	**29·5**	**0·0631**
Efficacy of a primary schedule with booster (R3R)																
Intention-to-treat population	**Month 32**				**Month 44**				**SE early**				**SE late**			
Site	**VE (%)**	**LL**	**UL**	**p-value**	**VE (%)**	**LL**	**UL**	**p-value**	**VE (%)**	**LL**	**UL**	**p-value**	**VE (%)**	**LL**	**UL**	**p-value**
Kilifi	100	-138	100	0·1203												
Korogwe									3·3	-7492	98·8	1·0000				
Manhiça	-24·4	-348	64·2	0·7820	26·6	-141	79·0	0·5944					-4·0	-210	64·4	1·0000
Lambaréné	37·2	-34·9	72·0	0·1978	22·5	-158	79·6	0·7333	0·0	-234	70·1	1·0000	82·6	-29·6	99·6	0·0753
Bagamoyo	71·8	-48·2	97·1	0·1044				.								.
Lilongwe	18·9	-277	83·9	1·0000	100	-4381	100	1·0000					100	-4462	100	1·0000
Agogo	59·3	18·2	81·0	0·0049	44·4	-26·9	77·1	0·1652					-4·3	-136	53·9	1·0000
Kombewa	21·1	-28·9	52·2	0·3106	-10·3	-67·0	27·1	0·4608	65·3	-5·9	90·4	0·0295	-8·9	-68·6	29·5	0·7183
Kintampo	19·8	-15·5	44·4	0·1878	31·9	-11·0	58·9	0·0653	30·2	-19·7	59·5	0·1187	16·9	-28·1	46·5	0·3260
Nanoro	54·2	22·6	73·7	0·0007	37·8	-9·9	65·6	0·0623	44·9	3·8	69·1	0·0028	41·6	9·8	62·8	0·0010
Siaya	31·6	-2·8	54·9	0·0309	15·3	-21·4	41·0	0·2521	40·3	-102	86·1	0·3136	3·1	-41·0	33·4	0·9096
Overall	**34·8**	**21·4**	**46·0**	**<0·0001**	**19·3**	**1·7**	**33·9**	**0·0187**	**29·9**	**3·9**	**49·2**	**0·0179**	**16·1**	**-1·4**	**30·6**	**0·0436**

VE (%) = vaccine efficacy (conditional method).
LL = lower limit of the 95% confidence interval.
UL = upper limit of the 95% confidence interval.
P-value = two-sided Fisher exact test.
Month 32 = cross sectional survey at 32 months post dose 1.
Month 44 = cross sectional survey at 44 months post dose 1.

SE early = study end in subjects having done Month 32 visit > 30 June 2012 (median follow-up in 5-17 months: 14 months post Month 32).
SE late = study end in subjects having done Month 32 visit ≤ 30 June 2012 (median follow-up in 5-17 months: 17 months post Month 32).

Table S15. Anthropometric findings in children in the 5-17 months age category (intention-to-treat population).

Study timepoint	Characteristics	Parameters	R3R		R3C		C3C	
			N	Value	N	Value	N	Value
Month 32	Height [cm]	N	2363	2351	2382	2367	2392	2377
		Missing	2363	12	2382	15	2392	15
		Mean	2363	94·7	2382	94·5	2392	94·4
		SD	2363	4·6	2382	4·8	2392	4·7
		Minimum	2363	72·0	2382	79·0	2392	79·0
		Maximum	2363	112·0	2382	110·0	2392	109·0
	Height for age Z-score	N	2363	2351	2382	2367	2392	2377
		Missing	2363	12	2382	15	2392	15
		Mean	2363	-1·3	2382	-1·4	2392	-1·4
		SD	2363	1·0	2382	1·0	2392	1·0
		Minimum	2363	-7·0	2382	-5·1	2392	-5·2
		Maximum	2363	2·1	2382	2·8	2392	2·3
	Weight for age Z-score	N	2363	2361	2382	2381	2392	2383
		Missing	2363	2	2382	1	2392	9
		Mean	2363	-0·9	2382	-1·0	2392	-1·0
		SD	2363	0·9	2382	0·9	2392	0·9
		Minimum	2363	-5·4	2382	-4·2	2392	-4·3
		Maximum	2363	2·5	2382	1·7	2392	1·6
	Mid upper arm circumference Z-score	N	2363	2361	2382	2379	2392	2390
		Missing	2363	2	2382	3	2392	2
		Mean	2363	-0·4	2382	-0·4	2392	-0·4
		SD	2363	0·9	2382	0·9	2392	0·8
		Minimum	2363	-5·3	2382	-4·1	2392	-3·4
		Maximum	2363	2·7	2382	3·5	2392	2·2
Month 44	Height [cm]	N	1275	1270	1289	1287	1307	1300
		Missing	1275	5	1289	2	1307	7
		Mean	1275	101·9	1289	101·6	1307	101·6
		SD	1275	4·8	1289	4·7	1307	4·8
		Minimum	1275	82·0	1289	85·0	1307	85·0
		Maximum	1275	116·0	1289	116·0	1307	118·0
	Height for age Z-score	N	1275	1270	1289	1287	1307	1300
		Missing	1275	5	1289	2	1307	7
		Mean	1275	-1·1	1289	-1·2	1307	-1·2
		SD	1275	1·0	1289	0·9	1307	1·0
		Minimum	1275	-5·3	1289	-5·2	1307	-4·6
		Maximum	1275	1·9	1289	1·9	1307	1·9
	Weight for age Z-score	N	1275	1274	1289	1288	1307	1306
		Missing	1275	1	1289	1	1307	1
		Mean	1275	-0·9	1289	-1·0	1307	-0·9
		SD	1275	0·9	1289	0·9	1307	0·8
		Minimum	1275	-3·8	1289	-4·0	1307	-4·2
		Maximum	1275	1·6	1289	1·7	1307	2·0
	Mid upper arm circumference Z-score	N	1275	1218	1289	1246	1307	1242
		Missing	1275	57	1289	43	1307	65
		Mean	1275	-0·7	1289	-0·7	1307	-0·6
		SD	1275	0·8	1289	0·9	1307	0·8
		Minimum	1275	-3·0	1289	-3·3	1307	-3·9
		Maximum	1275	1·9	1289	2·2	1307	2·0

Study timepoint	Characteristics	Parameters	R3R		R3C		C3C	
			N	Value	N	Value	N	Value
SE early	Height [cm]	N	774	769	755	748	768	765
		Missing	774	5	755	7	768	3
		Mean	774	102·1	755	102·0	768	102·0
		SD	774	5·4	755	5·6	768	5·4
		Minimum	774	83·0	755	87·0	768	84·0
		Maximum	774	118·0	755	119·0	768	120·0
	Height for age Z-score	N	774	769	755	748	768	765
		Missing	774	5	755	7	768	3
		Mean	774	-1·3	755	-1·3	768	-1·3
		SD	774	1·0	755	1·0	768	1·0
		Minimum	774	-5·5	755	-4·0	768	-5·0
		Maximum	774	1·9	755	1·4	768	2·0
	Weight for age Z-score	N	774	774	755	755	768	768
		Missing	774	0	755	0	768	0
		Mean	774	-1·0	755	-1·0	768	-1·0
		SD	774	0·8	755	0·8	768	0·8
		Minimum	774	-3·7	755	-3·5	768	-3·7
		Maximum	774	2·0	755	2·1	768	1·1
	Mid upper arm circumference Z-score	N	774	602	755	597	768	622
		Missing	774	172	755	158	768	146
		Mean	774	-0·8	755	-0·8	768	-0·8
		SD	774	0·9	755	0·9	768	0·8
		Minimum	774	-3·5	755	-3·6	768	-3·3
		Maximum	774	2·3	755	2·0	768	1·5
SE late	Height [cm]	N	1290	1275	1283	1270	1317	1305
		Missing	1290	15	1283	13	1317	12
		Mean	1290	105·5	1283	105·3	1317	105·0
		SD	1290	4·8	1283	4·9	1317	5·3
		Minimum	1290	87·0	1283	88·0	1317	41·0
		Maximum	1290	121·0	1283	121·0	1317	123·0
	Height for age Z-score	N	1290	1275	1283	1270	1317	1305
		Missing	1290	15	1283	13	1317	12
		Mean	1290	-1·0	1283	-1·1	1317	-1·1
		SD	1290	0·9	1283	0·9	1317	1·0
		Minimum	1290	-4·7	1283	-5·0	1317	-14·9
		Maximum	1290	2·0	1283	2·0	1317	2·1
	Weight for age Z-score	N	1290	1287	1283	1281	1317	1313
		Missing	1290	3	1283	2	1317	4
		Mean	1290	-0·9	1283	-1·0	1317	-1·0
		SD	1290	0·9	1283	0·9	1317	0·8
		Minimum	1290	-4·1	1283	-4·3	1317	-3·8
		Maximum	1290	1·9	1283	1·6	1317	1·6
	Mid upper arm circumference Z-score	N	1290	507	1283	548	1317	566
		Missing	1290	783	1283	735	1317	751
		Mean	1290	-0·7	1283	-0·8	1317	-0·7
		SD	1290	0·8	1283	0·9	1317	0·8
		Minimum	1290	-3·4	1283	-3·6	1317	-3·0
		Maximum	1290	1·8	1283	2·1	1317	1·8

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects.

SD = standard deviation.
Month 32 = cross sectional survey at 32 months post dose 1.
Month 44 = cross sectional survey at 44 months post dose 1.
SE early = study end in subjects having done Month 32 visit > 30 June 2012 (median follow-up in 5-17 months: 14 months post Month 32).
SE late = study end in subjects having done Month 32 visit ≤ 30 June 2012 (median follow-up in 5-17 months: 17 months post Month 32).

Table S16. Cumulative cases of clinical and severe malaria averted in each site and overall among children in the 5-17 months age category (intention-to-treat population).

Time period	Site	Clinical malaria (secondary case definition)		Severe malaria (secondary case definition)	
		Primary schedule without booster (R3C)	Primary schedule with booster (R3R)	Primary schedule without booster (R3C)	Primary schedule with booster (R3R)
M0-M21	Kilifi	35	35	0	0
	Korogwe	129	129	8	8
	Manhiça	116	116	13	13
	Lambaréné	305	305	25	25
	Bagamoyo	335	335	28	28
	Lilongwe	389	389	-3	-3
	Agogo	1518	1518	13	13
	Kombewa	1682	1682	38	38
	Kintampo	1867	1867	20	20
	Nanoro	2399	2399	7	7
	Siaya	3105	3105	50	50
	Overall	963	963	19	19
M0-M32	Kilifi	132	172	12	6
	Korogwe	151	126	15	11
	Manhiça	234	294	19	22
	Lambaréné	381	395	39	51
	Bagamoyo	424	538	28	28
	Lilongwe	533	604	-12	1
	Agogo	1779	2221	13	12
	Kombewa	1875	2451	30	34
	Kintampo	2474	3042	-31	11
	Nanoro	2983	3750	11	1
	Siaya	3847	4656	4	32
	Overall	1221	1475	12	20
M0-SE	Kilifi	250	303	12	6
	Korogwe	215	205	23	19
	Manhiça	341	236	24	27
	Lambaréné	498	472	54	57
	Bagamoyo	477	607	37	37
	Lilongwe	532	685	-17	6
	Agogo	2060	2722	8	25
	Kombewa	1937	2510	4	17
	Kintampo	2663	3892	-42	-15
	Nanoro	2897	4217	-8	-6
	Siaya	4443	6565	3	37
	Overall	1363	1774	8	19

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥37·5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre. This definition was used for this analysis as, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.
Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.
M0-SE = follow-up from day of dose 1 (Month 0) to study end (end of extension phase). For the 5-17 months age category SE= up to 48 months post dose 1.

Table S17. Overall vaccine efficacy against clinical and severe malaria among children in the 6-12 weeks age category (per-protocol population for efficacy).

Efficacy against clinical malaria (primary case definition) of a primary schedule without booster (R3C)												
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Per-protocol population for efficacy		N	n	T (year)	n/T	N	n	T (year)	n/T	(%)	95% CI		p-value
Clinical malaria	M2·5-SE	2005	5072	5322·9	0·95	2007	5666	5264·6	1·08	18·2	11·4	24·5	<0·0001
	M2·5-M32	2005	3856	4396·8	0·88	2007	4479	4343·8	1·03	20·4	13·5	26·8	<0·0001
	M2·5-M20*	3996	3848	5396·8	0·71	2007	2464	2674·0	0·92	26·6	20·3	32·4	<0·0001
	M21-M32	1788	1942	1687·0	1·15	1762	2012	1671·0	1·2	8·5	-0·6	16·7	0·0652
	M33-SE	1548	1216	926·4	1·31	1546	1187	921·9	1·29	3·9	-7·6	14·1	0·4905
	M21-SE	1788	3158	2613·1	1·21	1762	3199	2591·8	1·23	8·1	-0·4	15·9	0·0622
Efficacy against severe malaria (primary case definition) of a primary schedule without booster (R3C)													
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Per-protocol population for efficacy		N	n	Proportion affected		N	n	Proportion affected		(%)	95% CI		p-value
Severe malaria	M2·5-SE	2005	89	0·04		2007	102	0·05		12·7	-17·2	35·0	0·3737
	M2·5-M32	2005	79	0·04		2007	89	0·04		11·1	-21·7	35·2	0·4782
	M2·5-M20*	3996	100	0·03		2007	59	0·03		14·9	-19·5	38·9	0·3486
	M21-M32	1788	35	0·02		1762	38	0·02		9·2	-47·6	44·3	0·7234
	M33-SE	1548	13	0·01		1546	14	0·01		7·3	-113	59·9	0·8498
	M21-SE	1788	46	0·03		1762	51	0·03		11·1	-35·1	41·7	0·6071
Efficacy against clinical malaria (primary case definition) of a primary schedule with booster (R3R)													
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Per-protocol population for efficacy		N	n	T (year)	n/T	N	n	T (year)	n/T	(%)	95% CI		p-value
Clinical malaria	M2·5-SE	1985	4532	5245·2	0·86	2007	5666	5264·6	1·08	26·7	20·5	32·4	<0·0001
	M2·5-M32	1985	3466	4339·5	0·8	2007	4479	4343·8	1·03	28·4	22·1	34·2	<0·0001
	M2·5-M20*	3996	3848	5396·8	0·71	2007	2464	2674·0	0·92	26·6	20·3	32·4	<0·0001
	M21-M32	1743	1520	1662·3	0·91	1762	2012	1671·0	1·2	30·3	23·0	37·0	<0·0001
	M33-SE	1516	1069	907·4	1·18	1546	1187	921·9	1·29	12·4	1·9	21·7	0·0217
	M21-SE	1743	2586	2568·0	1·01	1762	3199	2591·8	1·23	25·9	18·8	32·4	<0·0001
Efficacy against severe malaria (primary case definition) of a primary schedule with booster (R3R)													
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Per-protocol population for efficacy		N	n	Proportion affected		N	n	Proportion affected		(%)	95% CI		p-value
Severe malaria	M2·5-SE	1985	80	0·04		2007	102	0·05		20·7	-7·3	41·6	0·1289
	M2·5-M32	1985	73	0·04		2007	89	0·04		17·1	-14·3	40·0	0·2300

	M2·5-M20*	3996	100	0·03	2007	59	0·03	14·9	-19·5	38·9	0·3486
	M21-M32	1743	23	0·01	1762	38	0·02	38·8	-5·4	65·2	0·0700
	M33-SE	1516	11	0·01	1546	14	0·01	19·9	-90·0	67·1	0·6892
	M21-SE	1743	33	0·02	1762	51	0·03	34·6	-3·3	59·1	0·0602
Incremental efficacy against clinical malaria (primary case definition) of a booster dose											
		R3R				**R3C**				**Point estimate of VE unadjusted for covariates**			
Per-protocol population for efficacy		**N**	**n**	**T (year)**	**n/T**	**N**	**n**	**T (year)**	**n/T**	**(%)**	**95% CI**		**p-value**
Clinical malaria	M21-SE	1743	2586	2568·0	1·01	1788	3158	2613·1	1·21	19·5	11·5	26·8	<0·0001
	M21-M32	1743	1520	1662·3	0·91	1788	1942	1687·0	1·15	24·0	15·7	31·5	<0·0001

*Data from previous analysis (comparing R3R+R3C versus C3C).
R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects.
n (clinical malaria) = number of episodes meeting the case definition.
n (severe malaria) = number of subjects reporting at least one event in each group.
T = person years at risk.
n/T = incidence rate.
Proportion affected = proportion of subjects reporting at least one event.
VE = vaccine efficacy (negative binomial model for clinical malaria; 1-relative risk for severe malaria).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.
M2·5-M20 = follow-up from 14 days post dose 3 (Month 2·5) to 18 months post dose 3 (Month 20).
M21-M32 = follow-up from day of booster dose to 30 months post dose 3 (Month 32).
M33-SE = follow-up from start of extension phase to study end (end of extension phase).
M2·5-SE = follow-up from 14 days post dose 3 (Month 2·5) to study end (end of extension phase).
M21-SE = follow-up from day of booster dose to study end (end of extension phase).
SE = study end (the median follow-up in the 6-12 weeks was 38 months post dose 1).
Clinical malaria primary case definition = illness in a child brought to a study facility with a measured temperature of ≥ 37·5°C and *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria.
Severe malaria primary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.
For clinical malaria: p-value from negative binomial regression.
For severe malaria: p-value from two-sided Fisher exact test.

Table S18. Overall vaccine efficacy against clinical and severe malaria secondary case definition among infants in the 6-12 weeks age category (intention-to-treat population).

Efficacy against clinical malaria (secondary case definition) of a primary schedule without booster (R3C)													
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**T (year)**	**n/T**	**N**	**n**	**T (year)**	**n/T**	**(%)**	**95% CI**		**p-value**
Clinical malaria	M0-SE	2178	8146	6071·3	1·34	2179	9146	6031·9	1·52	18·1	11·8	23·9	<0·0001
	M0-M32	2178	6315	5109·2	1·24	2179	7327	5068·7	1·45	19·6	13·3	25·5	<0·0001
Efficacy against severe malaria (secondary case definition) of a primary schedule without booster (R3C)													
		R3C				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**Proportion affected**		**N**	**n**	**Proportion affected**		**(%)**	**95% CI**		**p-value**
Severe malaria	M0-SE	2178	110	0·05		2179	129	0·06		14·7	-10·9	34·5	0·2310
	M0-M32	2178	97	0·04		2179	112	0·05		13·4	-14·7	34·7	0·3210
Efficacy against clinical malaria (secondary case definition) of a primary schedule with booster (R3R)													
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**T (year)**	**n/T**	**N**	**n**	**T (year)**	**n/T**	**(%)**	**95% CI**		**p-value**
Clinical malaria	M0-SE	2180	7420	6063·1	1·22	2179	9146	6031·9	1·52	27·1	21·4	32·4	<0·0001
	M0-M32	2180	5757	5099·6	1·13	2179	7327	5068·7	1·45	28·3	22·6	33·6	<0·0001
Efficacy against severe malaria (secondary case definition) of a primary schedule with booster (R3R)													
		R3R				C3C				Point estimate of VE unadjusted for covariates			
Intention-to-treat population		**N**	**n**	**Proportion affected**		**N**	**n**	**Proportion affected**		**(%)**	**95% CI**		**p-value**
Severe malaria	M0-SE	2180	108	0·05		2179	129	0·06		16·3	-8·9	35·8	0·1614
	M0-M32	2180	99	0·05		2179	112	0·05		11·6	-16·8	33·3	0·3600

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects.
n (clinical malaria) = number of episodes meeting the case definition.
n (severe malaria) = number of subjects reporting at least one event in each group.
T = person years at risk.
n/T = incidence rate.
Proportion affected = proportion of subjects reporting at least one event.
VE = vaccine efficacy (negative binomial model for clinical malaria; 1-relative risk for severe malaria).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.
M0-SE = follow-up from day of dose 1 (Month 0) to study end (end of extension phase).
M0-M32 = follow-up from day of dose 1 (Month 0) to 32 months post dose 1 (Month 32).

SE = study end (the median follow-up in the 6-12 weeks was 38 months post dose 1).
Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥37.5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre. This definition was used for this analysis as, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.
Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.
For clinical malaria: p-value from negative binomial regression.
For severe malaria: p-value from two-sided Fisher exact test.

Table S19. Overall vaccine efficacy against incident severe malaria anaemia, malaria hospitalization and fatal malaria until the end of the extension phase (M0-SE) among infants in the 6-12 weeks age category (intention-to-treat population).

Efficacy of a primary schedule without booster (R3C)										
		R3C			C3C			Point estimate of VE unadjusted for covariates			
Intention-to-treat population		N	n	Proportion affected	N	n	Proportion affected	(%)	95% CI		p-value
Incident severe malaria anaemia	Case definition 1	2178	31	0·01	2179	35	0·02	11·4	-47·9	47·2	0·7101
	Case definition 2	2178	39	0·02	2179	40	0·02	2·5	-556	38·9	1·0000
Malaria hospitalization	Case definition 1	2178	167	0·08	2179	188	0·09	11·1	-10·1	28·3	0·2680
	Case definition 2	2178	199	0·09	2179	222	0·10	10·3	-9·1	26·3	0·2593
Fatal malaria	Primary case definition	2178	0	0	2179	0	0				
	Secondary case definition	2178	2	0	2179	2	0	0·0	-1280	92·7	1·0000
	ICD10 code	2178	12	0·01	2179	6	0	-100·1	-550	30·5	0·1661
Efficacy of a primary schedule with booster (R3R)											
		R3R			C3C			Point estimate of VE unadjusted for covariates			
Intention-to-treat population		N	n	Proportion affected	N	n	Proportion affected	(%)	95% CI		p-value
Incident severe malaria anaemia	Case definition 1	2180	24	0·01	2179	35	0·02	31·5	-18·5	61·0	0·1522
	Case definition 2	2180	27	0·01	2179	40	0·02	32·5	-12·7	60·2	0·1114
Malaria hospitalization	Case definition 1	2180	142	0·07	2179	188	0·09	24·5	5·6	39·7	0·0084
	Case definition 2	2180	175	0·08	2179	222	0·1	21·2	3·5	35·7	0·0134
Fatal malaria	Primary case definition	2180	0	0	2179	0	0				
	Secondary case definition	2180	4	0	2179	2	0	-99·9	-2110	71·3	0·6873
	ICD10 code	2180	8	0	2179	6	0	-33·3	-366	59·4	0·7902

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects included in each group (without missing values).
n = number of subjects reporting at least one event in each group.
Proportion affected = proportion of subjects reporting at least one event.
VE (%) = vaccine efficacy (conditional method).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.
P-value = two-sided Fisher exact test.
M0-SE = follow-up from day of dose 1 (Month 0) to study end (end of extension phase). The median follow-up in the 6-12 weeks age category was 38 months post dose 1.

Incident severe malaria anaemia case definition 1 = a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 5000 parasites per cubic millimetre.
Incident severe malaria anaemia case definition 2 = a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 0 parasites per cubic millimetre.
Malaria hospitalization case definition 1 = a medical hospitalization with confirmed *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre.
Malaria hospitalization case definition 2 = a hospitalization which, in the judgment of the principal investigator, *P. falciparum* infection was the sole or a major contributing factor to the presentation.
Fatal malaria primary definition = a case of severe malaria meeting the primary case definition of severe malaria with a fatal outcome.
Fatal malaria secondary case definition = a case of severe malaria meeting the secondary case definition of severe malaria with a fatal outcome.
Fatal malaria (ICD10 code) = a fatal case associated with International Classification Disease (ICD10) code B50, B53, B54.

Table S20. Overall vaccine efficacy against serious illnesses until the end of the extension phase (M0-SE) among infants in the 6-12 weeks age category (intention-to-treat population).

Efficacy of a primary schedule without booster (R3C)										
		R3C			C3C			Point estimate of VE unadjusted for covariates		
Intention-to-treat population		N	n	Proportion affected	N	n	Proportion affected	(%)	95% CI	p-value
Bacteraemia	Case definition 1	2178	56	0·03	2179	52	0·02	-7·7	-60·3 27·5	0·6982
	Case definition 2 (Salmonella sepsis)	2178	36	0·02	2179	34	0·02	-5·9	-74·5 35·6	0·8111
Pneumonia	Primary case definition	2178	124	0·06	2179	137	0·06	9·4	-16·3 29·6	0·4437
	Secondary case definition 1	2178	37	0·02	2179	30	0·01	-23·4	-107 25·8	0·3924
All-cause hospitalization	Primary case definition	2178	549	0·25	2179	567	0·26	3·1	-9·1 14·0	0·5552
All-cause mortality	Case definition 1	2178	54	0·02	2179	42	0·02	-28·6	-97·3 15·6	0·2177
	Case definition 2	2178	51	0·02	2179	40	0·02	-27·6	-98·0 17·3	0·2463
Blood transfusions	-	2178	75	0·03	2179	88	0·04	14·7	-17·4 38·2	0·3381
Efficacy of a primary schedule with booster (R3R)										
		R3R			C3C			Point estimate of VE unadjusted for covariates		
Intention-to-treat population		N	n	Proportion affected	N	n	Proportion affected	(%)	95% CI	p-value
Bacteraemia	Case definition 1	2180	53	0·02	2179	52	0·02	-1·9	-52·3 31·8	1·0000
	Case definition 2 (Salmonella sepsis)	2180	27	0·01	2179	34	0·02	20·6	-35·5 53·9	0·3707
Pneumonia	Primary case definition	2180	135	0·06	2179	137	0·06	1·5	-25·8 22·9	0·9005
	Secondary case definition 1	2180	36	0·02	2179	30	0·01	-19·9	-102 28·2	0·5355
All-cause hospitalization	Primary case definition	2180	528	0·24	2179	567	0·26	6·9	-5·0 17·5	0·1733
All-cause mortality	Case definition 1	2180	51	0·02	2179	42	0·02	-21·4	-87·2 20·9	0·4018
	Case definition 2	2180	49	0·02	2179	40	0·02	-22·4	-90·8 21·0	0·3917
Blood transfusions	-	2180	73	0·03	2179	88	0·04	17·1	-14·4 40·0	0·2296

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects included in each group (without missing values).
n = number of subjects reporting at least one event in each group.
Proportion affected = proportion of subjects reporting at least one event.
VE(%) = vaccine efficacy (conditional method).
95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

P-value = two-sided Fisher exact test.
M0-SE = follow-up from day of dose 1 (Month 0) to study end (end of extension phase). The median follow-up in the 6-12 weeks age category was 38 months post dose 1.
Bacteraemia case definition 1 = a child with a positive blood culture taken within 72 hours of admission.
Bacteraemia case definition 2 (Salmonella sepsis) = a child with a positive salmonella blood culture taken within 72 hours of admission.
Pneumonia primary case definition = cough or difficulty breathing (on history) and tachypnea (≥ 50 breaths per minute < 1 year, ≥ 40 breaths per minute ≥ 1year) and lower chest wall indrawing.
Pneumonia secondary case definition 1 = a case of pneumonia meeting the primary case definition of pneumonia with chest x-ray consolidation or pleural effusion on x-ray taken within 72 h of admission.
All-cause hospitalization primary case definition = a medical hospitalization of any cause, excluding planned admissions for medical investigation/care or elective surgery and trauma.
All-cause mortality case definition 1 = a fatality of any cause, including mortality in the community and in hospital.
All-cause mortality case definition 2 = a fatality of medical cause, including mortality in the community and in hospital and excluding trauma, which may be diagnosed by verbal autopsy.
Blood transfusion = a child with inpatient admission with documented blood transfusion.

Table S21. Vaccine efficacy against prevalent parasitaemia until the end of the extension phase among infants in the 6-12 weeks age category (intention-to-treat population).

Efficacy of a primary schedule without booster (R3C)								
Intention-to-treat population	**Month 32**				**SE early**			
Site	**VE (%)**	**LL**	**UL**	**p-value**	**VE (%)**	**LL**	**UL**	**p-value**
Kilifi	100	-4254	100	1·0000				
Korogwe	100	-3496	100	0·4798				
Manhiça*					19·1	-276	83·9	1·0000
Lambaréné	-127·3	-1205	43·3	0·2281	-533·3	-29E3	23·2	0·0528
Bagamoyo	-25·6	-420	68·1	0·7671				
Lilongwe	-217·6	-1017	-9·7	0·0209	-483·7	-5320	-27·4	0·0098
Agogo	21·2	-51·5	59·7	0·5146	-17·6	-155	45·6	0·7087
Kombewa	7·4	-53·1	43·9	0·7861	6·8	-57·1	44·7	0·7804
Kintampo	2·3	-132	59·2	1·0000	-39·6	-159	23·5	0·1818
Nanoro	-16·7	-87·4	27·0	0·5256	7·4	-32·0	35·1	0·5902
Siaya	23·3	-17·4	50·2	0·1549	18·6	-21·2	45·4	0·2527
Overall	**-4·2**	**-29·1**	**15·8**	**0·6954**	**-7·1**	**-30·5**	**12·1**	**0·4601**
Efficacy of a primary schedule with booster (R3R)								
Intention-to-treat population	**Month 32**				**SE early**			
Site	**VE (%)**	**LL**	**UL**	**p-value**	**VE (%)**	**LL**	**UL**	**p-value**
Kilifi	100	-4466	100	1·0000				
Korogwe	11·0	-6888	98·9	1·0000				
Manhiça*					-78·0	-576	46·4	0·4048
Lambaréné	45·4	-377	95·4	0·6560	-100·0	-12E3	89·6	1·0000
Bagamoyo	14·3	-298	83·0	1·0000				
Lilongwe	-159·5	-840	14·9	0·0820	-171·7	-2754	55·5	0·2675
Agogo	20·8	-50·8	59·0	0·5196	10·1	-103	60·6	0·8455
Kombewa	5·0	-57·6	42·7	0·8911	13·2	-47·6	49·0	0·5721
Kintampo	3·2	-127	58·7	1·0000	33·8	-34·8	68·2	0·1959
Nanoro	38·4	-8·4	65·8	0·0612	28·9	-5·0	52·2	0·0315
Siaya	4·2	-43·2	35·9	0·8197	29·6	-6·4	53·8	0·0471
Overall	**5·3**	**-17·9**	**23·9**	**0·6071**	**18·2**	**-1·0**	**33·8**	**0·0451**

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
VE (%) = vaccine efficacy (conditional method).
LL = lower limit of the 95% confidence interval.
UL = upper limit of the 95% confidence interval.
P-value = two-sided Fisher exact test.
Month 32 = cross sectional survey at 32 months post dose 1.
SE early = study end in subjects having done Month 32 visit > 30 June 2012 (median follow-up in 6-12 weeks: 7 months post Month 32).
* In Manhiça, for the cross sectional visit performed at Month 32, parasite prevalence was detected in three subjects in R3C, six subjects in R3R and zero subject in C3C. Because there was no parasite prevalence in the control group the VE cannot be calculated.

Table S22. Anthropometric findings in infants in the 6-12 weeks age category (intention-to-treat population).

Study timepoint	Characteristics	Parameters	R3R		R3C		C3C	
			N	Value	N	Value	N	Value
Month 32	Height [cm]	N	1726	1709	1731	1716	1725	1709
		Missing	1726	17	1731	15	1725	16
		Mean	1726	88·5	1731	88·6	1725	88·5
		SD	1726	4·0	1731	4·0	1725	4·1
		Minimum	1726	69·0	1731	75·0	1725	70·0
		Maximum	1726	105·0	1731	101·0	1725	102·0
	Height for age Z-score	N	1726	1709	1731	1716	1725	1709
		Missing	1726	17	1731	15	1725	16
		Mean	1726	-1·5	1731	-1·4	1725	-1·5
		SD	1726	1·1	1731	1·1	1725	1·1
		Minimum	1726	-7·1	1731	-5·2	1725	-6·3
		Maximum	1726	2·6	1731	2·0	1725	2·4
	Weight for age Z-score	N	1726	1725	1731	1731	1725	1724
		Missing	1726	1	1731	0	1725	1
		Mean	1726	-0·9	1731	-0·9	1725	-0·9
		SD	1726	1·0	1731	1·0	1725	1·0
		Minimum	1726	-5·0	1731	-4·5	1725	-4·6
		Maximum	1726	2·2	1731	3·0	1725	1·9
	Mid upper arm circumference Z-score	N	1726	1726	1731	1731	1725	1725
		Missing	1726	0	1731	0	1725	0
		Mean	1726	-0·4	1731	-0·3	1725	-0·4
		SD	1726	0·9	1731	1·0	1725	1·0
		Minimum	1726	-3·9	1731	-3·4	1725	-3·8
		Maximum	1726	2·9	1731	4·3	1725	2·9
SE early	Height [cm]	N	1555	1507	1533	1493	1549	1500
		Missing	1555	48	1533	40	1549	49
		Mean	1555	93·3	1533	93·4	1549	93·2
		SD	1555	4·6	1533	4·6	1549	4·6
		Minimum	1555	70·0	1533	78·0	1549	72·0
		Maximum	1555	109·0	1533	111·0	1549	109·0
	Height for age Z-score	N	1555	1507	1533	1493	1549	1500
		Missing	1555	48	1533	40	1549	49
		Mean	1555	-1·4	1533	-1·4	1549	-1·4
		SD	1555	1·0	1533	1·0	1549	1·0
		Minimum	1555	-7·5	1533	-5·2	1549	-6·2
		Maximum	1555	2·1	1533	2·5	1549	2·2
	Weight for age Z-score	N	1555	1552	1533	1531	1549	1547
		Missing	1555	3	1533	2	1549	2
		Mean	1555	-0·9	1533	-0·9	1549	-0·9
		SD	1555	0·9	1533	0·9	1549	0·9
		Minimum	1555	-4·9	1533	-4·5	1549	-4·7
		Maximum	1555	2·1	1533	2·5	1549	1·7
	Mid upper arm circumference Z-score	N	1555	1555	1533	1533	1549	1548
		Missing	1555	0	1533	0	1549	1
		Mean	1555	-0·5	1533	-0·4	1549	-0·5
		SD	1555	0·9	1533	0·9	1549	0·9
		Minimum	1555	-3·2	1533	-3·5	1549	-3·5
		Maximum	1555	2·6	1533	3·7	1549	2·5

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects.
SD = standard deviation.
Month 32 = cross sectional survey at 32 months post dose 1.
SE early = study end in subjects having done Month 32 visit > 30 June 2012 (median follow-up in 6-12 weeks: 7 months post Month 32).

Table S23. Cumulative cases of clinical and severe malaria averted in each site and overall in infants in the 6-12 weeks age category (intention-to-treat population).

Time period	Site	Clinical malaria (secondary case definition)		Severe malaria (secondary case definition)	
		Primary schedule without booster (R3C)	Primary schedule with booster (R3R)	Primary schedule without booster (R3C)	Primary schedule with booster (R3R)
M0-M21	Kilifi	-9	-9	0	0
	Korogwe	70	70	-3	-3
	Manhiça	146	146	-10	-10
	Lambaréné	9	9	-25	-25
	Bagamoyo	142	142	21	21
	Lilongwe	421	421	-8	-8
	Agogo	443	443	-13	-13
	Kombewa	970	970	36	36
	Kintampo	263	263	2	2
	Nanoro	993	993	21	21
	Siaya	1814	1814	12	12
	Overall	518	518	5	5
M0-M32	Kilifi	4	-25	-11	-12
	Korogwe	68	177	-3	3
	Manhiça	193	214	-11	-28
	Lambaréné	-50	314	1	0
	Bagamoyo	173	211	25	25
	Lilongwe	479	679	7	3
	Agogo	570	915	-17	-18
	Kombewa	1095	1105	74	39
	Kintampo	36	781	-43	-20
	Nanoro	1101	2165	10	26
	Siaya	1853	2921	-1	49
	Overall	526	873	5	9
M0-SE	Kilifi	27	-30	-11	-12
	Korogwe	114	190	-9	3
	Manhiça	218	179	17	0
	Lambaréné	-140	268	-31	0
	Bagamoyo	277	309	40	40
	Lilongwe	493	772	3	3
	Agogo	585	1077	-17	-12
	Kombewa	1144	1404	59	51
	Kintampo	-172	726	-43	-62
	Nanoro	1367	2428	10	19
	Siaya	2178	3406	13	56
	Overall	558	983	8	12

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥37·5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre. This definition was used for this analysis as, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.
Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.
M0-SE = follow-up from day of dose 1 (Month 0) to study end (end of extension phase). For the 6-12 weeks, SE= up to 39 months post dose 1.

Table S24. Seropositivity rates and geometric means titres for anti-CS antibodies at Month 20, Month 32, Month 44 and study end in children in the 5-17 months age category (per-protocol population for immunogenicity).

Group	Timing		Seropositivity (≥ 0·5 EU/mL)				GMT				
					95% CI			95% CI			
		N	n	%	LL	UL	value	LL	UL	Min	Max
R3R	PIII(M20)	442	440	99·5	98·4	99·9	34·4	30·7	38·6	<0·5	666·7
	PIV(M21)	426	425	99·8	98·7	100	318·2	295·1	343·0	<0·5	2733·0
	PIV(M32)	414	414	100	99·1	100	52·4	47·8	57·6	2·2	444·0
	PIV(M44)	103	103	100	96·5	100	33·0	26·9	40·3	1·8	398·7
	SE	104	104	100	96·5	100	25·4	20·6	31·2	1·1	220·8
R3C	PIII(M20)	438	434	99·1	97·7	99·8	35·4	31·7	39·5	<0·5	863·4
	PIV(M21)	425	421	99·1	97·6	99·7	34·2	30·5	38·3	<0·5	715·0
	PIV(M32)	408	404	99·0	97·5	99·7	19·3	17·2	21·8	<0·5	447·9
	PIV(M44)	101	99	98·0	93·0	99·8	16·8	13·5	21·0	<0·5	201·6
	SE	99	97	98·0	92·9	99·8	14·4	11·4	18·1	<0·5	150·2
C3C	PIII(M20)	426	34	8·0	5·6	11·0	0·3	0·3	0·3	<0·5	51·6
	PIV(M21)	409	34	8·3	5·8	11·4	0·3	0·3	0·3	<0·5	403·9
	PIV(M32)	393	46	11·7	8·7	15·3	0·3	0·3	0·3	<0·5	21·6
	PIV(M44)	86	15	17·4	10·1	27·1	0·3	0·3	0·4	<0·5	5·2
	SE	98	10	10·2	5·0	18·0	0·3	0·3	0·4	<0·5	7·1

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
Anti-CS = anti-circumsporozoite protein antibodies.
GMT = geometric mean antibody titre calculated on all subjects.
EU/mL = ELISA unit per millilitre.
N = number of subjects with available results.
n/% = number/percentage of subjects with titre equal to or above specified value.
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit.
Min/Max = minimum/maximum.
PIII(M20) = 18 months post dose 3.
PIV(M21) = 1 month post booster dose.
PIV(M32) = 12 months post booster dose.
PIV(M44) = 24 months post booster dose.
SE = Study end.

Table S25. Seropositivity rates and geometric means titres for anti-CS antibodies at Month 20, Month 32 and study end in infants in the 6-12 weeks age category (per-protocol population for immunogenicity).

Group	Timing		Seropositivity (≥ 0·5 EU/mL)				GMT				
					95% CI			95% CI			
		N	n	%	LL	UL	value	LL	UL	Min	Max
R3R	PIII(M20)	530	491	92·6	90·1	94·7	5·9	5·2	6·7	<0·5	205·1
	PIV(M21)	503	501	99·6	98·6	100	169·9	153·8	187·7	<0·5	3454·6
	PIV(M32)	478	465	97·3	95·4	98·5	15·9	13·8	18·3	<0·5	268·3
	SE	101	95	94·1	87·5	97·8	8·9	6·5	12·3	<0·5	139·0
R3C	PIII(M20)	569	529	93·0	90·6	94·9	6·6	5·8	7·5	<0·5	169·3
	PIV(M21)	544	501	92·1	89·5	94·2	6·2	5·4	7·0	<0·5	325·7
	PIV(M32)	515	466	90·5	87·6	92·9	3·7	3·3	4·2	<0·5	128·7
	SE	103	94	91·3	84·1	95·9	2·6	2·0	3·4	<0·5	68·5
C3C	PIII(M20)	554	56	10·1	7·7	12·9	0·3	0·3	0·3	<0·5	97·1
	PIV(M21)	519	47	9·1	6·7	11·9	0·3	0·3	0·3	<0·5	481·0
	PIV(M32)	501	67	13·4	10·5	16·7	0·3	0·3	0·3	<0·5	16·7
	SE	131	20	15·3	9·6	22·6	0·3	0·3	0·4	<0·5	8·6

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
Anti-CS = anti-circumsporozoite protein antibodies.
GMT = geometric mean antibody titre calculated on all subjects.
EU/mL = ELISA unit per millilitre.
N = number of subjects with available results.
n/% = number/percentage of subjects with titre equal to or above specified value.
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit.
Min/Max = minimum/maximum.
PIII(M20) = 18 months post dose 3.
PIV(M21) = 1 month post booster dose.
PIV(M32) = 12 months post booster dose.
PIV(M44) = 24 months post booster dose.
SE = study end.

Table S26. Incidence of solicited local and general symptoms within seven days post booster dose among children in the 5-17 months age category (intention-to-treat population).

Local symptoms																
		R3R (RTS,S/AS01)					R3C (Menjugate)					C3C (Menjugate)				
					95% CI					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	641	109	17·0	14·2	20·1	639	45	7·0	5·2	9·3	633	41	6·5	4·7	8·7
	Grade 3	641	0	0·0	0·0	0·6	639	0	0·0	0·0	0·6	633	0	0·0	0·0	0·6
Redness	All	641	15	2·3	1·3	3·8	639	13	2·0	1·1	3·5	633	8	1·3	0·5	2·5
	>20 mm	641	3	0·5	0·1	1·4	639	0	0·0	0·0	0·6	633	0	0·0	0·0	0·6
Swelling	All	641	42	6·6	4·8	8·8	639	35	5·5	3·8	7·5	633	30	4·7	3·2	6·7
	>20 mm	641	9	1·4	0·6	2·6	639	1	0·2	0·0	0·9	633	0	0·0	0·0	0·6
General symptoms																
		R3R					R3C					C3C				
					95% CI					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	641	55	8·6	6·5	11·0	639	22	3·4	2·2	5·2	633	21	3·3	2·1	5·0
	Grade 3	641	1	0·2	0·0	0·9	639	0	0·0	0·0	0·6	633	0	0·0	0·0	0·6
	Related	641	34	5·3	3·7	7·3	639	10	1·6	0·8	2·9	633	13	2·1	1·1	3·5
	Grade 3 Related	641	0	0·0	0·0	0·6	639	0	0·0	0·0	06	633	0	0·0	0·0	0·6
Irritability	All	641	63	9·8	7·6	12·4	639	25	3·9	2·5	5·7	633	18	2·8	1·7	4·5
	Grade 3	641	1	0·2	0·0	0·9	639	0	0·0	0·0	0·6	633	0	0·0	0·0	0·6
	Related	641	40	6·2	4·5	8·4	639	12	1·9	1·0	3·3	633	8	1·3	0·5	2·5
	Grade 3 Related	641	1	0·2	0·0	0·9	639	0	0·0	0·0	06	633	0	0·0	0·0	0·6
Loss of appetite	All	641	66	10·3	8·1	12·9	639	27	4·2	2·8	6·1	633	21	3·3	2·1	5·0
	Grade 3	641	1	0·2	0·0	0·9	639	0	0·0	0·0	0·6	633	0	0·0	0·0	0·6
	Related	641	39	6·1	4·4	8·2	639	14	2·2	1·2	3·6	633	13	2·1	1·1	3·5
	Grade 3 Related	641	1	0·2	0·0	0·9	639	0	0·0	0·0	06	633	0	0·0	0·0	0·6
Temperature (axillary)	All (≥37·5°C)	641	233	36·3	32·6	40·2	639	70	11·0	8·6	13·6	633	45	7·1	5·2	9·4
	>39·0°C	641	34	5·3	3·7	7·3	639	6	0·9	0·3	2·0	633	5	0·8	0·3	1·8
	Related	641	151	23·6	20·3	27·0	639	29	4·5	3·1	6·5	633	16	2·5	1·5	4·1
	>39·0°C Related	641	24	3·7	2·4	5·5	639	1	0·2	0·0	09	633	0	0·0	0·0	0·6

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects with the administered dose.
n/% = number/percentage of subjects reporting the symptom at least once.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.
Fever was defined as an axillary temperature ≥37·5°C and grade 3 fever as an axillary temperature >39·0°C.

Table S27. Incidence of solicited local and general symptoms within seven days post booster dose among infants in the 6-12 weeks age category (intention-to-treat population).

Local symptoms																
		R3R (RTS,S/AS01)					R3C (Menjugate)					C3C (Menjugate)				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	608	59	9·7	7·5	12·3	625	29	4·6	3·1	6·6	621	25	4·0	2·6	5·9
	Grade 3	608	0	0·0	0·0	0·6	625	0	0·0	0·0	0·6	621	0	0·0	0·0	0·6
Redness	All	608	9	1·5	0·7	2·8	625	12	1·9	1·0	3·3	621	9	1·4	0·7	2·7
	>20 mm	608	1	0·2	0·0	0·9	625	0	0·0	0·0	0·6	621	0	0·0	0·0	0·6
Swelling	All	608	45	7·4	5·4	9·8	625	28	4·5	3·0	6·4	621	43	6·9	5·1	9·2
	>20 mm	608	5	0·8	0·3	1·9	625	0	0·0	0·0	0·6	621	2	0·3	0·0	1·2
General symptoms																
		R3R					R3C					C3C				
					95% CI					95% CI					95% CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Drowsiness	All	608	33	5·4	3·8	7·5	625	19	3·0	1·8	4·7	621	15	2·4	1·4	4·0
	Grade 3	608	0	0·0	0·0	0·6	625	0	0·0	0·0	0·6	621	0	0·0	0·0	0·6
	Related	608	19	3·1	1·9	4·8	625	6	1·0	0·4	2·1	621	5	0·8	0·3	1·9
	Grade 3 Related	608	0	0·0	0·0	0·6	625	0	0·0	0·0	0·6	621	0	0·0	0·0	0·6
Irritability	All	608	46	7·6	5·6	10·0	625	23	3·7	2·3	5·5	621	23	3·7	2·4	5·5
	Grade 3	608	0	0·0	0·0	0·6	625	0	0·0	0·0	0·6	621	0	0·0	0·0	0·6
	Related	608	27	4·4	2·9	6·4	625	10	1·6	0·8	2·9	621	6	1·0	0·4	2·1
	Grade 3 Related	608	0	0·0	0·0	0·6	625	0	0·0	0·0	0·6	621	0	0·0	0·0	0·6
Loss of appetite	All	608	45	7·4	5·4	9·8	625	27	4·3	2·9	6·2	621	18	2·9	1·7	4·5
	Grade 3	608	0	0·0	0·0	0·6	625	0	0·0	0·0	0·6	621	0	0·0	0·0	0·6
	Related	608	26	4·3	2·8	6·2	625	8	1·3	0·6	2·5	621	6	1·0	0·4	2·1
	Grade 3 Related	608	0	0·0	0·0	0·6	625	0	0·0	0·0	0·6	621	0	0·0	0·0	0·6
Temperature (axillary)	All (≥37·5°C)	608	152	25·0	21·6	28·6	625	52	8·3	6·3	10·8	621	58	9·3	7·2	11·9
	>39·0°C	608	9	1·5	0·7	2·8	625	7	1·1	0·5	2·3	621	10	1·6	0·8	2·9
	Related	608	80	13·2	10·6	16·1	625	15	2·4	1·3	3·9	621	18	2·9	1·7	4·5
	>39·0°C Related	608	5	0·8	0·3	1·9	625	1	0·2	0·0	0·9	621	3	0·5	0·1	1·4

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of subjects with the administered dose.
n/% = number/percentage of subjects reporting the symptom at least once.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.
Fever was defined as an axillary temperature ≥37·5°C and grade 3 fever as an axillary temperature >39·0°C.

Table S28. Incidence of seizures within seven days post booster dose in both age categories (intention-to-treat population).

5-17 months age category													
		R3R N = 2447				R3C N = 2472				C3C N = 2473			
				95% CI				95% CI				95% CI	
Characteristics	**Categories**	**n**	**n/1000**	**LL**	**UL**	**n**	**n/1000**	**LL**	**UL**	**n**	**n/1000**	**LL**	**UL**
Generalized convulsive seizure	Level 1 to 3	6	2·5	0·9	5·3	3	1·2	0·3	3·5	1	0·4	0·0	2·3
Convulsive seizure	Level 1 to 5	8	3·3	1·4	6·4	4	1·6	0·4	4·1	1	0·4	0·0	2·3
Diagnostic certainty level	Level 1	1	0·4	0·0	2·3	1	0·4	0·0	2·3	0	-	0·0	1·5
	Level 2	5	2·0	0·7	4·8	2	0·8	0·1	2·9	1	0·4	0·0	2·3
	Level 3	0	0·0	0·0	1·5	0	0·0	0·0	1·5	0	0·0	0·0	1·5
	Level 4	1	0·4	0·0	2·3	0	-	0.0	1·5	0	-	0·0	1·5
	Level 5	1	0·4	0·0	2·3	1	0·4	0·0	2·3	0	-	0·0	1·5
6-12 weeks age category													
		R3R N = 1825				R3C N = 1837				C3C N = 1827			
				95% CI				95% CI				95% CI	
Characteristics	**Categories**	**n**	**n/1000**	**LL**	**UL**	**n**	**n/1000**	**LL**	**UL**	**n**	**n/1000**	**LL**	**UL**
Generalized convulsive seizure	Level 1 to 3	4	2·2	0·6	5·6	0	-	0·0	2·0	1	0·5	0·0	3·0
Convulsive seizure	Level 1 to 5	4	2·2	0·6	5·6	0	-	0·0	2·0	1	0·5	0·0	3·0
Diagnostic certainty level	Level 1	1	0·5	0·0	3·0	0	-	0·0	2·0	0	-	0·0	2·0
	Level 2	3	1·6	0·3	4·8	0	-	0·0	2·0	1	0·5	0·0	3·0
	Level 3	0	0·0	0·0	2·0	0	0·0	0·0	2·0	0	0·0	0·0	2·0
	Level 4	0	0·0	0·0	2·0	0	0·0	0·0	2·0	0	0·0	0·0	2·0
	Level 5	0	0·0	0·0	2·0	0	0·0	0·0	2·0	0	0·0	0·0	2·0

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
N = number of doses.
n = number of doses in a given category.
n/1000 = n / number of doses with available results x 1000.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.
Level 1 = witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations.
Level 2 = history of unconsciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations.
Level 3 = history of unconsciousness AND other generalized motor manifestations.
Level 4 = reported generalized convulsive seizure with insufficient evidence to meet the case definition.
Level 5 = not a case of generalized convulsive seizure.

Table S29. Percentage of subjects reporting unsolicited adverse events within 30 days post booster dose with an incidence greater or equal to 5% among children in the 5-17 months age category (intention-to-treat population).

		R3R N = 641				R3C N = 639				C3C N = 633			
				95% CI				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one AE		232	36·2	32·5	40·0	205	32·1	28·5	35·9	215	34·0	30·3	37·8
At least one AE excluding malaria		211	32·9	29·3	36·7	180	28·2	24·7	31·8	181	28·6	25·1	32·3
General disorders and administration site conditions	Pyrexia	44	6·9	5·0	9·1	10	1·6	0·8	2·9	7	1·1	0·4	2·3
Infections and infestations	Malaria	49	7·6	5·7	10 0	53	8·3	6·3	10·7	84	13·3	10·7	16·2
	Upper respiratory tract infection	61	9·5	7·4	12·1	55	8·6	6·5	11·1	55	8·7	6·6	11·2

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
At least one AE = at least one AE experienced (regardless of the MedDRA Preferred Term).
At least one AE excluding malaria = at least one AE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.
N = number of subjects with booster dose administered.
n/% = number/percentage of subjects reporting the AE at least once.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S30. Percentage of subjects reporting unsolicited adverse events within 30 days post each vaccination with an incidence greater or equal to 5% among children in the 5-17 months age category (intention-to-treat population).

		R3R N = 740				R3C N = 739				C3C N = 721			
				95% CI				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one AE		646	87·3	84·7	89·6	653	88·4	85·8	90·6	637	88·3	85·8	90·6
At least one AE excluding malaria		634	85·7	82·9	88·1	645	87·3	84·7	89·6	621	86·1	83·4	88·6
Blood and lymphatic system disorders	Anaemia	32	4·3	3·0	6·1	28	3·8	2·5	5·4	36	5·0	3·5	6·8
Gastrointestinal disorders	Diarrhoea	87	11·8	9·5	14·3	109	14·7	12·3	17·5	92	12·8	10·4	15·4
	Enteritis	66	8·9	7·0	11·2	72	9·7	7·7	12·1	65	9·0	7·0	11·3
General disorders and administration site conditions	Pyrexia	151	20·4	17·6	23·5	117	15·8	13·3	18·7	75	10·4	8·3	12·9
Infections and infestations	Bronchitis	38	5·1	3·7	7·0	46	6·2	4·6	8·2	37	5·1	3·6	7·0
	Conjunctivitis	66	8·9	7·0	11·2	61	8·3	6·4	10·5	74	10·3	8·1	12·7
	Gastroenteritis	203	27·4	24·2	30·8	190	25·7	22·6	29·0	179	24·8	21·7	28·1
	Malaria	163	22·0	19·1	25·2	154	20·8	18·0	23·9	224	31·1	27·7	34·6
	Nasopharyngitis	58	7·8	6·0	10·0	61	8·3	6·4	10·5	61	8·5	6·5	10·7
	Pneumonia	95	12·8	10·5	15·5	85	11·5	9·3	14·0	78	10·8	8·6	13·3
	Rhinitis	70	9·5	7·4	11·8	53	7·2	5·4	9·3	52	7·2	5·4	9·4
	Upper respiratory tract infection	335	45·3	41·6	48·9	351	47·5	43·8	51·2	345	47·9	44·1	51·6
Respiratory, thoracic and mediastinal disorders	Cough	57	7·7	5·9	9·9	62	8·4	6·5	10·6	47	6·5	4·8	8·6

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
At least one AE = at least one AE experienced (regardless of the MedDRA Preferred Term).
At least one AE excluding malaria = at least one AE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.
N = number of subjects with at least one administered dose.
n/% = number/percentage of subjects reporting the AE at least once.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S31. Percentage of subjects reporting unsolicited adverse events within 30 days post booster dose with an incidence greater or equal to 5% among infants in the 6-12 weeks age category (intention-to-treat population).

		R3R N = 608				R3C N = 625				C3C N = 621			
				95% CI				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one AE		231	38·0	34·1	42·0	239	38·2	34·4	42·2	240	38·6	34·8	42·6
At least one AE excluding malaria		211	34·7	30·9	38·6	221	35·4	31·6	39·3	222	35·7	32·0	39·7
Infections and infestations	Gastroenteritis	34	5·6	3·9	7·7	29	4·6	3·1	6·6	40	6·4	4·6	8·7
	Malaria	44	7·2	5·3	9·6	56	9·0	6·8	11·5	55	8·9	6·7	11·4
	Upper respiratory tract infection	87	14·3	11·6	173	93	14·9	12·2	17·9	90	14·5	11·8	17·5

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
At least one AE = at least one AE experienced (regardless of the MedDRA Preferred Term).
At least one AE excluding malaria = at least one AE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.
N = number of subjects with booster dose administered.
n/% = number/percentage of subjects reporting the AE at least once.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S32. Percentage of subjects reporting unsolicited adverse events within 30 days post each vaccination with an incidence greater or equal to 5% among infants in the 6-12 weeks age category (intention-to-treat population).

		R3R N = 725				R3C N = 737				C3C N = 738			
				95% CI				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one AE		597	82·3	79·4	85·1	618	83·9	81·0	86·4	632	85·6	82·9	88·1
At least one AE excluding Malaria		588	81·1	78·1	83·9	611	82·9	80·0	85·6	630	85·4	82·6	87·8
Gastrointestinal disorders	Enteritis	86	11·9	9·6	14·4	63	8·5	6·6	10·8	81	11·0	8·8	13·5
General disorders and administration site conditions	Pyrexia	131	18·1	15·3	21·1	137	18·6	15·8	21·6	121	16·4	13·8	19·3
Infections and infestations	Bronchitis	37	5·1	3·6	7·0	32	4·3	3·0	6·1	33	4·5	3·1	6·2
	Conjunctivitis	72	9·9	7·9	12·3	67	9·1	7·1	11·4	81	11·0	8·8	13·5
	Gastroenteritis	133	18·3	15·6	21·4	134	18·2	15·5	21·2	155	21·0	18·1	24·1
	Malaria	88	12·1	9·8	14·7	120	16·3	13·7	19·1	114	15·4	12·9	18·3
	Nasopharyngitis	51	7·0	5·3	9·1	54	7·3	5·6	9·5	61	8·3	6·4	10·5
	Otitis media	32	4·4	3·0	6·2	42	5·7	4·1	7·6	41	5·6	4·0	7·5
	Pneumonia	53	7·3	5·5	9·5	56	7·6	5·8	9·8	44	6·0	4·4	7·9
	Rhinitis	83	11·4	9·2	14·0	83	11·3	9·1	13·8	94	12·7	10·4	15·4
	Upper respiratory tract infection	326	45·0	41·3	48·7	333	45·2	41·5	48·9	347	47·0	43·4	50·7

R3R = RTS,S/AS01 primary schedule with booster.
R3C = RTS,S/AS01 primary schedule without booster.
C3C = control group.
At least one AE = at least one AE experienced (regardless of the MedDRA Preferred Term).
At least one AE excluding malaria = at least one AE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.
N = number of subjects with at least one administered dose.
n/% = number/percentage of subjects reporting the AE at least once.
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S33. Grading of solicited adverse events

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	Absent
	1	Minor reaction to touch
	2	Cries/protests on touch
	3	Cries when limb is moved/spontaneously painful
Swelling at injection site	0	Absent
	1	<5 mm
	2	5-20 mm
	3	>20 mm
Redness at injection site	0	Absent
	1	<5 mm
	2	5-20 mm
	3	>20 mm
Fever	0	<37.5°C
	1	37.5-38°C
	2	>38-39°C
	3	>39°C
Irritability/Fussiness	0	Behaviour as usual
	1	Crying more than usual/ no effect on normal activity
	2	Crying more than usual/ interferes with normal activity
	3	Crying that cannot be comforted/ prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Drowsiness easily tolerated
	2	Drowsiness that interferes with normal activity
	3	Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Eating less than usual/ no effect on normal activity
	2	Eating less than usual/ interferes with normal activity
	3	Not eating at all